PSI Webinar

Development of Gene Therapies:

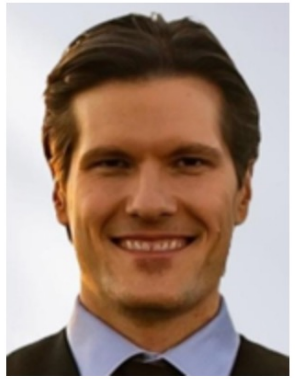
Strategic, Scientific, Regulatory and Access Considerations

Avery McIntosh, PhD
Oleksandr Sverdlov, PhD

07 August 2024

About Us

Speaker details

Speaker	Biography
 *Avery McIntosh*	Avery McIntosh, PhD is a drug developer working in internal medicine and rare disease at Pfizer. He received his MSc and PhD in biostatistics from Boston University with a dissertation on Bayesian methods to model household tuberculosis transmission. He has managed teams of statisticians across study phases and in a variety of drug types and disease areas, including neurology, ophthalmology, infectious disease/global health, hematology, and oncology. He has published peer-reviewed articles on various topics in drug development and biostatistics, including development of cell and gene therapies and qualification of digital endpoints in neurological diseases.
 *Oleksandr Sverdlov*	Oleksandr Sverdlov, PhD is a Neuroscience Disease Area Statistical Lead at Novartis. He earned his BSc in Applied Mathematics from V.N. Karazin Kharkiv National University, Ukraine, MSc in Statistics from University of Maryland, Baltimore County (UMBC), and PhD in Information Technology with Concentration in Statistical Science from George Mason University. He has been actively involved in methodological research and applications of innovative statistical approaches in drug development. He has co-authored over forty refereed articles, edited two monographs, and co-authored a book “Mathematical and Statistical Skills in the Biopharmaceutical Industry: A Pragmatic Approach” (CRC Press/Chapman & Hall, 2019). His most recent work involves design and analysis of clinical trials evaluating novel digital technologies.

Disclaimer

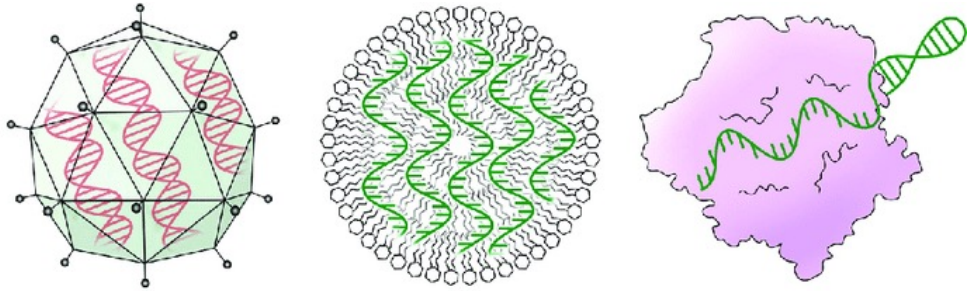
- The views and opinions expressed are solely our own
- No proprietary information is presented nor are any specific ongoing programs within our companies discussed
- The primary purpose of this talk is educational—it is intended to provide information on the speakers' thinking about gene therapy product development, and is not intended to advertise or promote any gene therapy products mentioned herein
- No conflicts of interest to disclose

Agenda

1. A Recent History of Gene Therapies (GTx)
    a) Scientific principles and mechanisms of action
    b) Overview of genetic diseases
    c) Principles of immunology
    d) Clinical pharmacology of GTx
    e) Regulatory designations for GTx
    f) Ethics
    g) Trajectory of product approval since 2012

2. Clinical Development of GTx
    a) Preclinical elements
    b) Trial design & analysis
    c) Challenges and opportunities in neurology
    d) Options for ultra-rare GTx development
    e) Dose finding
    f) Adaptive endpoints
    g) Long term follow-up / platform studies

Gene Therapies



"*Gene therapy is a technique that modifies a person's genes to treat or cure disease*." –FDA

Approach	Virus	Nanoparticle	Enzyme complex
Example	Adeno-associated virus (AAV) packaged with DNA encoding Cas9 & sgRNA	Liposomes encapsulating mRNA & sgRNA	Ribonucleoprotein (RNP) complex of Cas9 protein and sgRNA
Size	20 nm	50-500 nm	12 nm
Advantages	Extremely effective; prior use with classic gene therapy	Straightforward to prepare; low immunogenicity	Short lifetime and lower risk of off-target cutting

https://www.researchgate.net/publication/320339544_The_Promise_and_Challenge_of_In_Vivo_Delivery_for_Genome_Therapeutics

Major differences between cell/gene therapies and traditional pharmaceutical products (LMW/ other biologics):

- GTx are (so far) one-time administrations
- Source of safety signals is manifold: delivery mechanism, transgene insert, promoter, over/under expression
- ADME is a fundamentally different concept (biodistribution/shedding)
- CMC is major challenging for GTx
- Traditional study phases 1,2,3 often will not apply
- Dose finding is often constrained
- Often orphan, pediatric diseases, novel endpoints

FDA
Center for Biologics Evaluation and Research

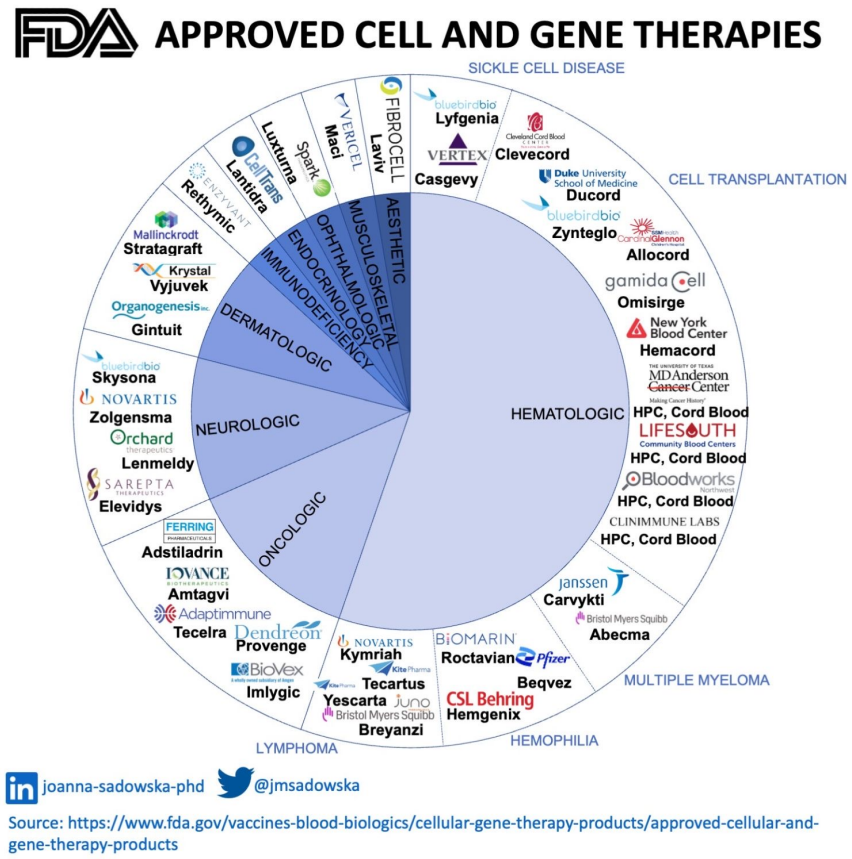
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Committee for Advanced Therapies (CAT)

Development Landscape

The majority of GTx to treat rare diseases in pipeline are oncology and neurology

www.asgct.org/publications/landscape-report



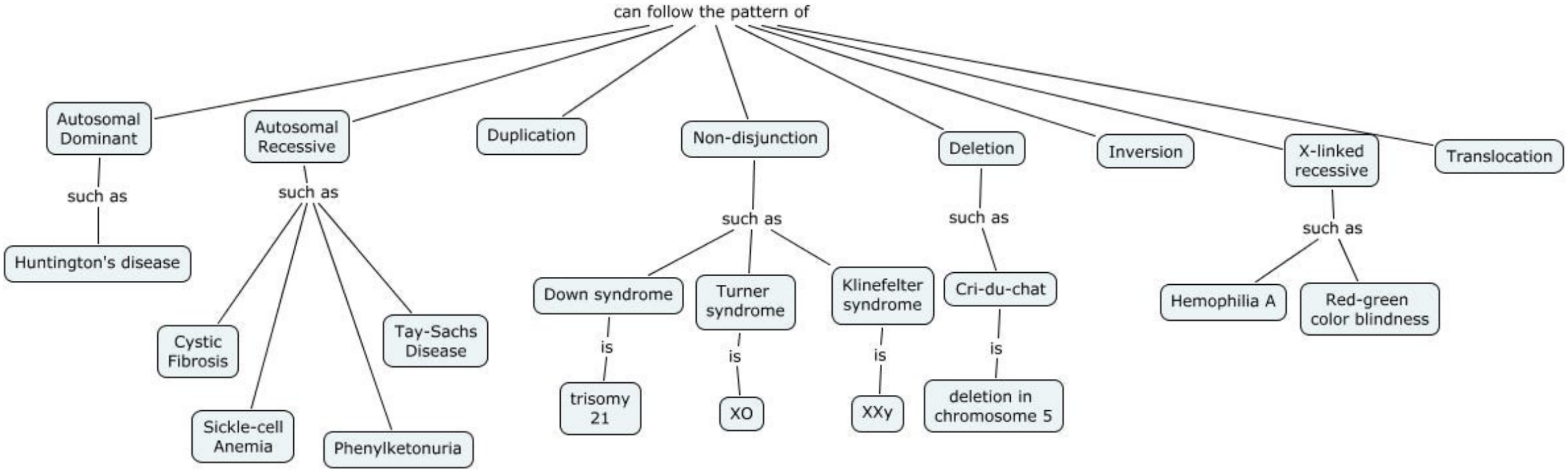
Source: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products

Global Status	Q1 2023	Q2 2023	Q3 2023	Q4 2023	Q1 2024
Preclinical	1,493	1,539	1,522	1,528	1,471
Phase I	245	240	256	270	301
Phase II	247	260	267	274	282
Phase III	30	30	30	33	35
Pre-registration	7	6	7	6	4
Total	**2,022**	**2,075**	**2,082**	**2,111**	**2,093**

Source: Pharmaprojects | Citeline, April 2024

Mechanisms of Genetic Disorders

The many ways genes can create disease means there is not just one *mechanism of action* for GTx



https://medium.com/the-21st-century/human-genetic-disorders-leading-cause-of-deaths-from-an-awareness-perspective-48c95dad9ee4

Example Genetic Disorders

July 7

HEALTH

‘It Will Consume Your Life’: 4 Families Take On Rare Diseases

Confronted by illnesses that most scientists overlook, these families had to work out their own approaches to find treatments.

By Gina Kolata

JUNE 23, 2020 | BRIAN BARRETT

My Friend Was Struck by ALS. To Fight Back, He Built a Movement

At 37, Brian Wallach was diagnosed with the fatal disease. So he tapped a lifetime of connections to give help and hope to fellow sufferers—while grappling with his own mortality.

May 6

HEALTH

First Patient Begins Newly Approved Sickle Cell Gene Therapy

A 12-year-old boy in the Washington, D.C., area faces months of procedures to remedy his disease. “I want to be cured,” he said.

By Gina Kolata and Kenny Holston

PRINT EDITION Hope for Sickle Cell Gene Therapy | May 14, 2024, Page D1

Jan. 23

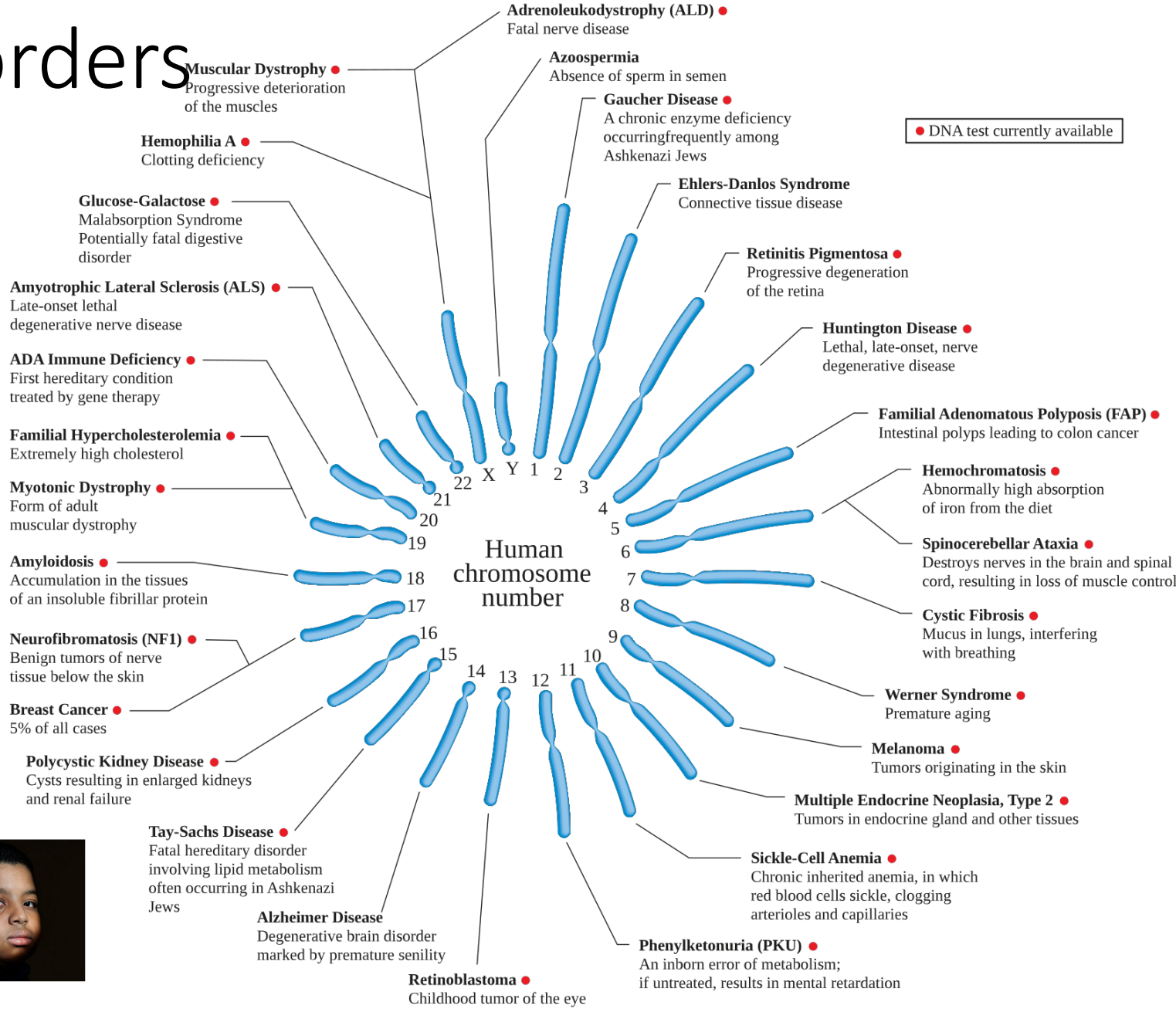
HEALTH

Gene Therapy Allows an 11-Year-Old Boy to Hear for the First Time

The genetic treatment targeted a particular kind of congenital deafness and will soon be tried in children who are younger.

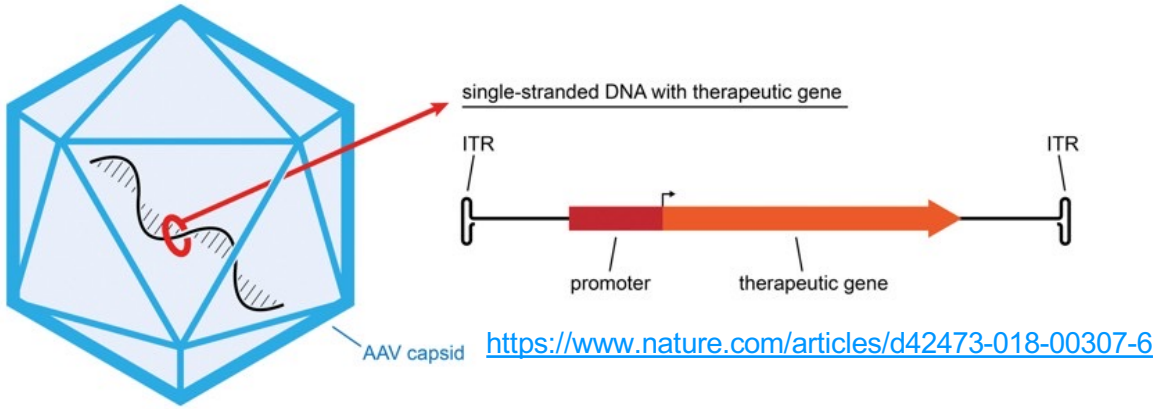
By Gina Kolata

PRINT EDITION Innovative Use of Gene Therapy Lets Boy Hear for the First Time | January 24, 2024, Page A1



By Ігор Петков - Own work, CC0, https://commons.wikimedia.org/w/index.php?curid=57928376

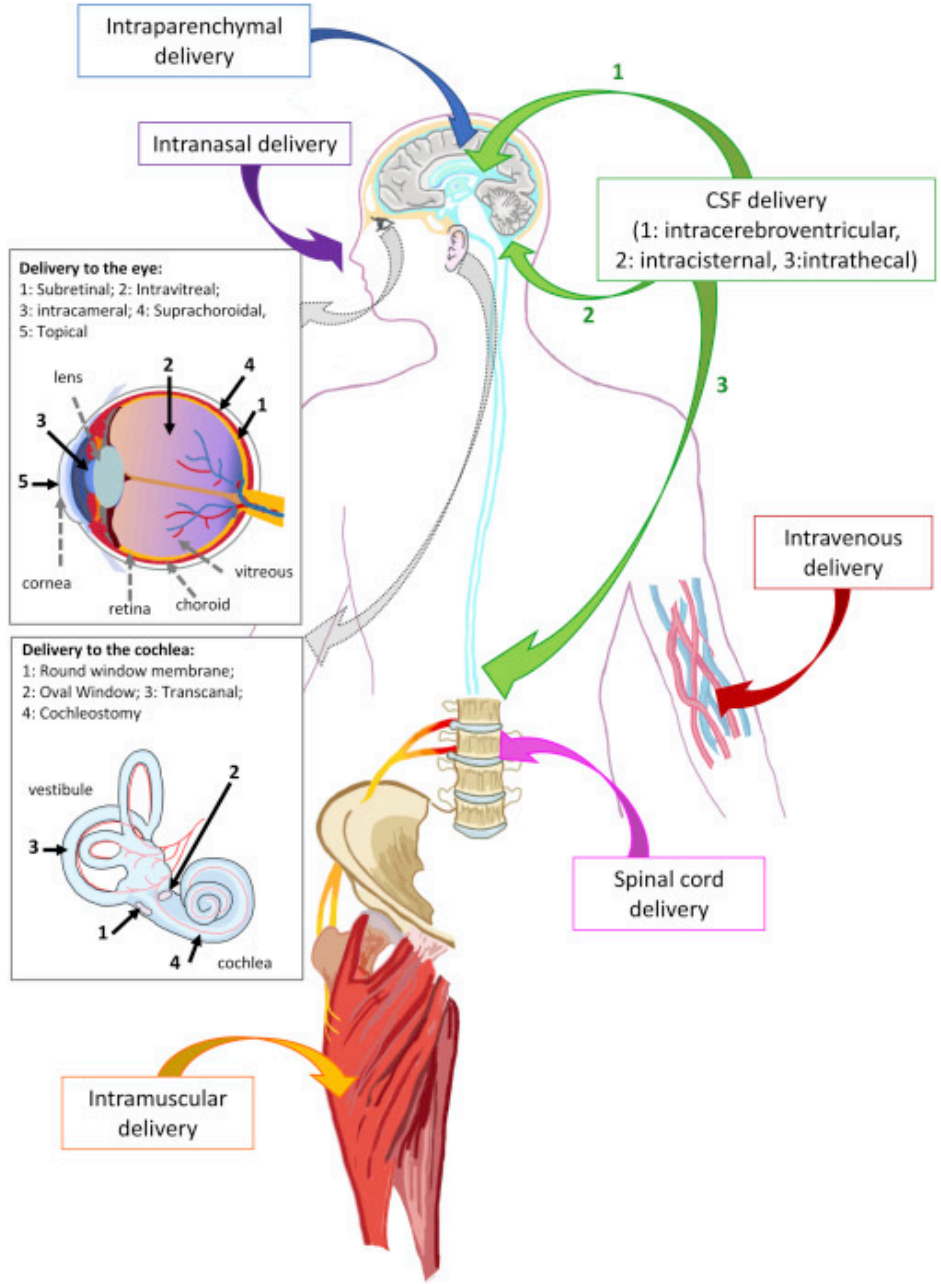
Target Tissue/ RoA/ MoA are Variable



https://www.nature.com/articles/d42473-018-00307-6

Goal is to get “normal” amount of protein expression in the appropriate cell

<u>Multiple MoAs</u> (gene replacement, gene/base editing, insertion/excision, knockdown, epigenetic, etc.)

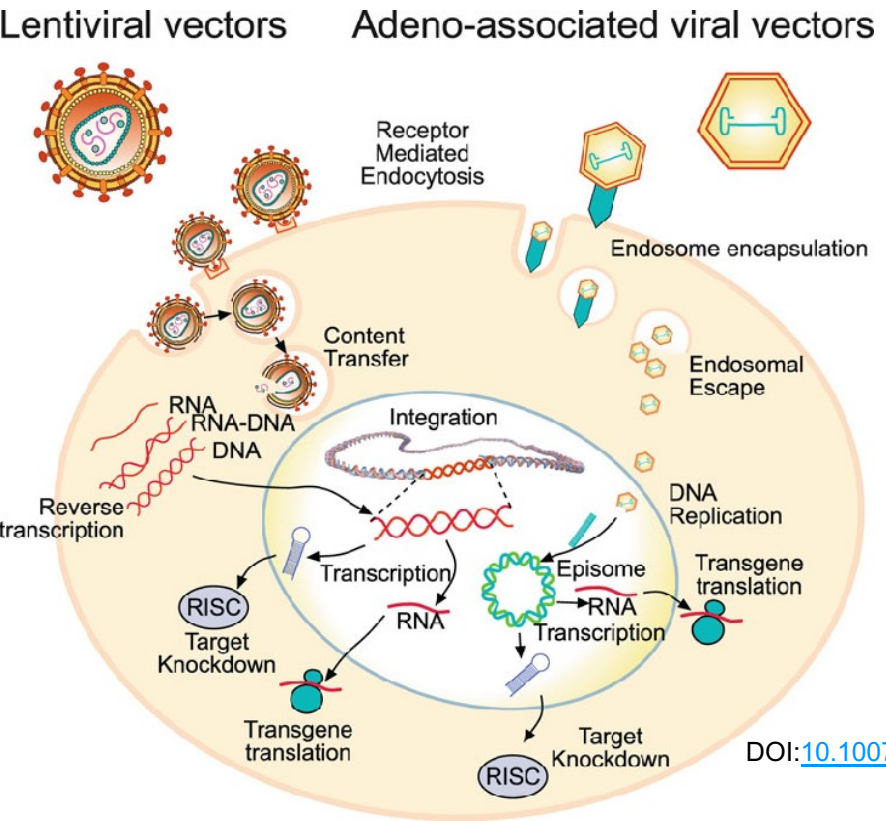


Hudrey E and Vendenberghe L. Neuron. 2019 Apr 3;102(1):263. doi: 10.1016/j.neuron.2019.03.020

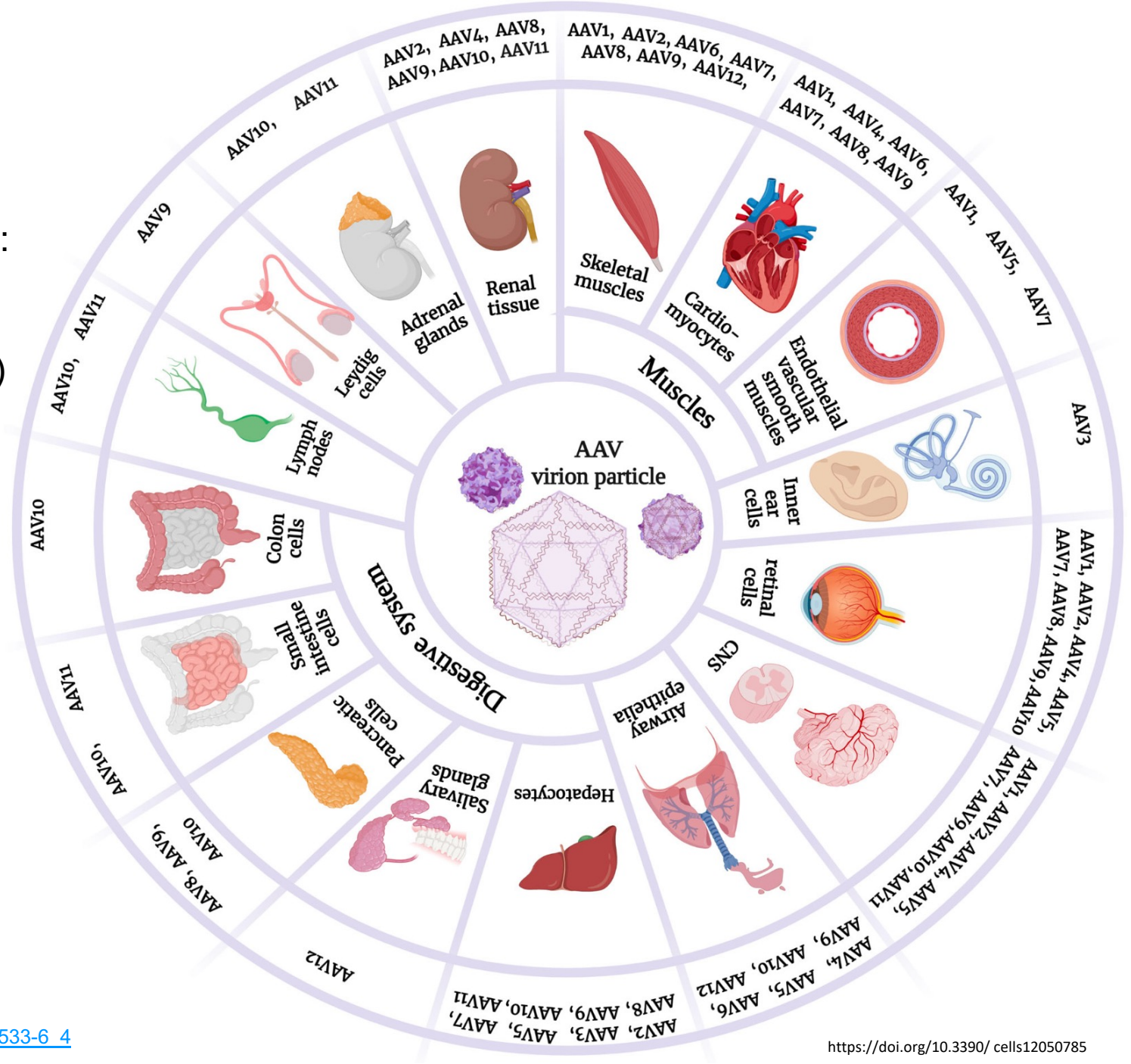
Vectors

For *in vivo* AAV GTx, different vector serotypes have different cell uptake affinities
(AAV8: subretinal, AAV9: neuronal tissue, AAV2: kidney, etc.), all naturally occurring serotypes

Very active space (capsid engineering)



DOI:10.1007/978-1-61779-533-6_4

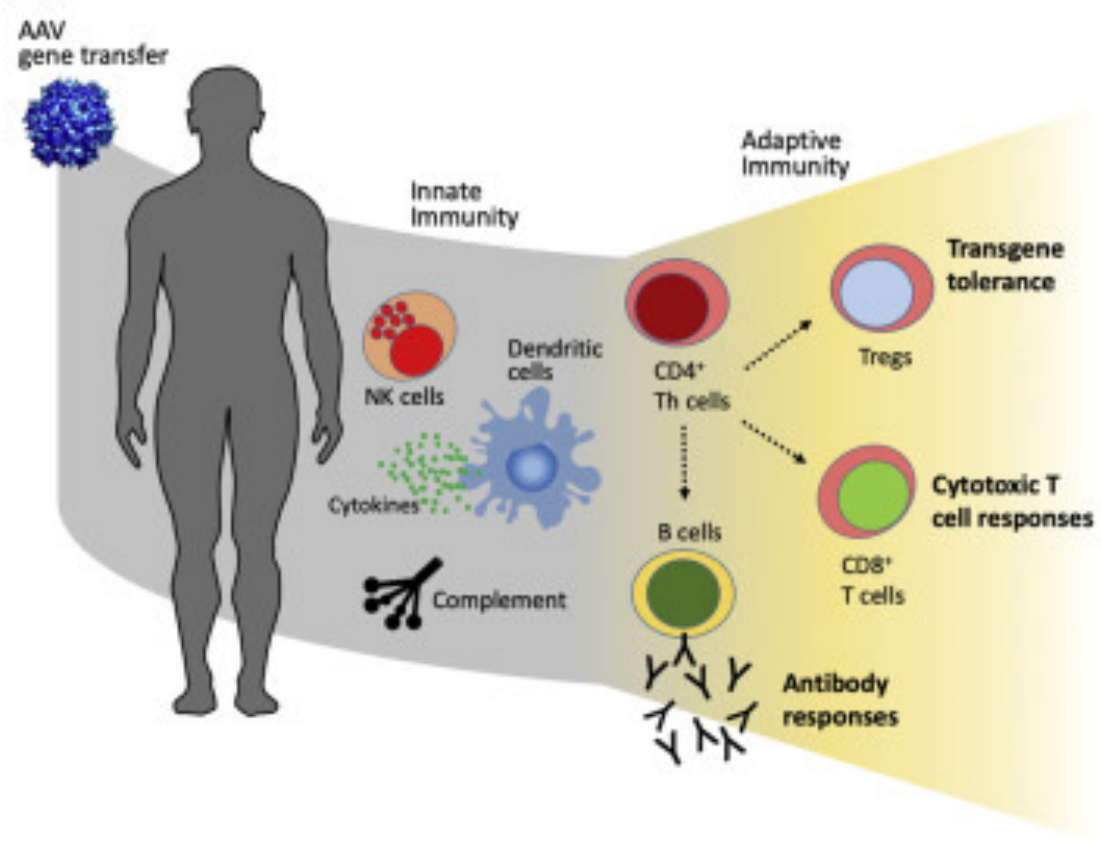


https://doi.org/10.3390/ cells12050785

Immunogenicity

- Immune response can be a safety or efficacy concern
  - If immune system attacks virus before transduction then the therapy is inactivated!
  - Could lead to exaggerated immune response
  - This can happen with GTx, biologics, even LMW drugs

- Pre-existing anti-AAV antibodies are measured prior to treatment and if level is too high, treatment may not be given
  - What constitutes “too high” is not settled
  - Dependent on the assay, so not comparable between trials



https://www.cell.com/molecular-therapy-family/molecular-therapy/fulltext/S1525-0016(20)30003-4

Immunogenicity (continued)

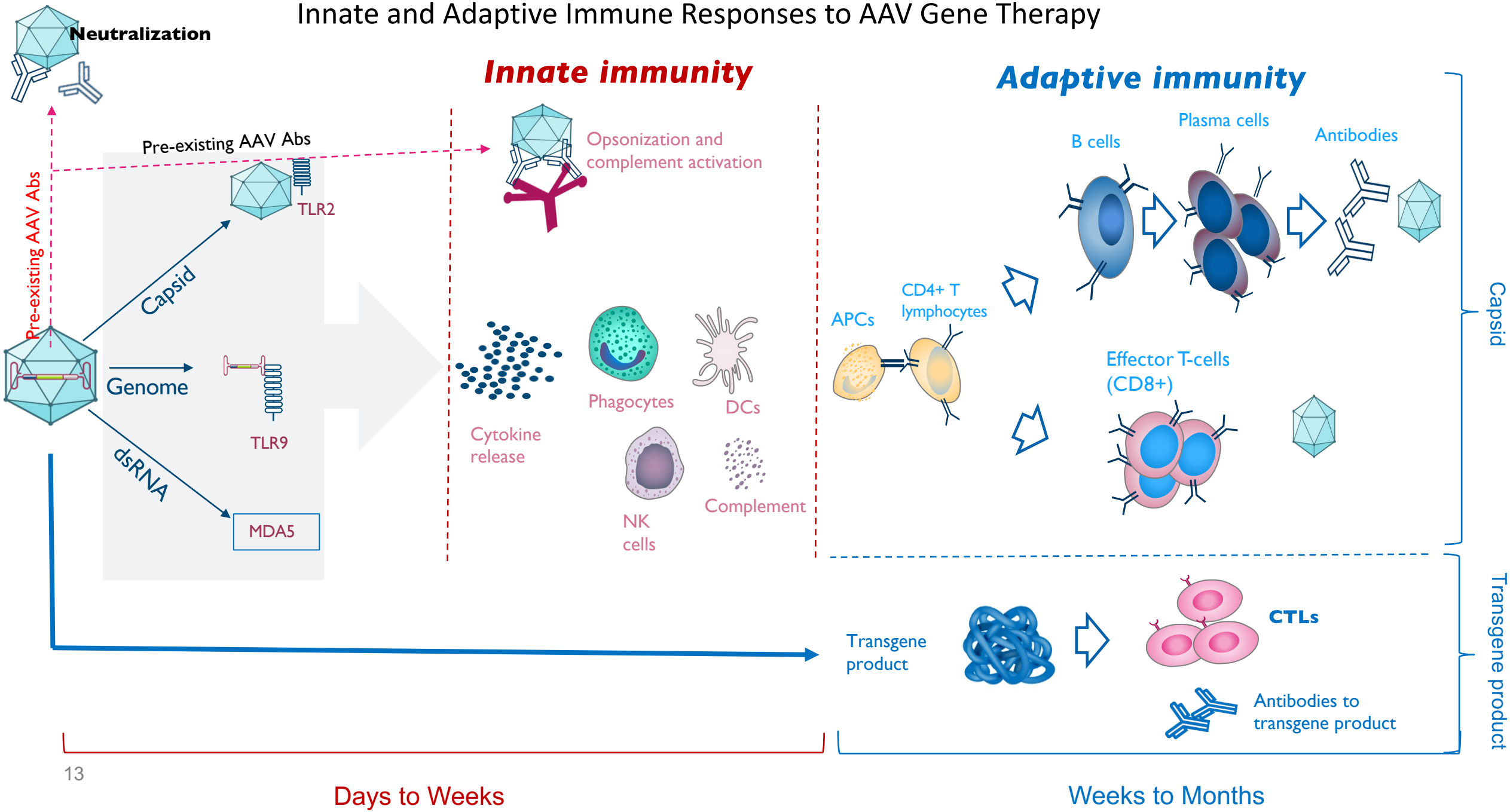
- Impact of pre-existing anti-AAV antibodies is route dependent (subretinal seems to have nothing really while intravenous is higher)

- Immunosuppressive drugs can be used prior to study drug administration
  - Rituximab, sirolimus, pegcetacoplan (?)
  - Other experimental approaches to immune modulation:
    - anti-FcRn antibodies that reduce IgG levels;
    - IgG cleaving enzymes from streptococcus pyrogenes (IdeS);
    - “cloaking”—encasing AAV in exosome to minimize interaction with NAbs;
    - immunoadsorption (depletion of anti-AAV IgGs with plasmapheresis)

- Anti-transgene antibodies are a possibility
  - Body can view endogenous proteins never before expressed as “foreign” and attack them

- Besides enormous cost, IG is why gene therapies are often one-time administrations

Innate and Adaptive Immune Responses to AAV Gene Therapy



Observed Immunotoxicities in AAV gene therapy trials

Clinical observation	**Mechanism**	**Potential mitigation strategies**	Reference
Transaminase elevation 1 week after rAAV administration	Innate immune response against the capsid and genome	Corticosteroid treatment, reduce CpG motif content in transgene, reduce expression in hepatocytes (tissue-specific promoter)	Day, 2021; Chand, J. Hepatol 2021
Transaminase elevation 3–12 weeks after rAAV administration	Cytotoxic T cell immune response against the AAV. peptides with associated liver inflammation	Corticosteroid treatment; Immunosuppressive drugs targeting T cells	Nathwani, 2014; Chand, J Hepatol 2021
Hepatic failure	Inflammatory T-cell immune response	Optimize vector tropism: enhance potency and specificity – reduce vector dose, reduce expression in hepatocytes	Feldman, 2020
Myositis/myocarditis	Anti-transgene immune response to expressed therapeutic protein	Exclude patients with deletions in dystrophin N-terminal epitopes present in the transgene	Bonneman, 2022
Thrombotic microangiopathy	Complement dysregulation	B cell depletion/sirolimus; Complement inhibition	Chand DH, J Pediatr. 2021
Thrombocytopenia / platelet reduction	Innate immune activation	Reduce vector dose; Complement inhibition	Day, 2021

Meriggioli, Matthew N. "*AAV Vector Immunogenicity in Gene Therapy: Mechanisms, Assessment, and Immunomodulation Strategies*." *Development of Gene Therapies*. Chapman and Hall/CRC, 2024. 147-176.

Immune Responses to AAV: Underlying Factors and Mitigation Strategies

	Capsid	Genome	Transgene product	Mitigation Strategies
Vector/transgene product	• PAMPs in AAV capsid	• Transgene DNA • ds-RNA • Self-complementary vs single stranded vector	• Therapeutic protein	• Capsid and genome engineering • Patient selection (AAV-exposed, CRIM – negative)
Innate Immunity	• Recognition of PAMPs in the AAV capsid via TLR2 binding	• Recognition of viral genome via TLR9 • dsRNA production driven (promoter activity of ITRs) – MDA5.	• ?	• Corticosteroids • Complement inhibition • Capsid and genome engineering
Humoral Immunity	• Treatment-emergent • Pre-existing	• None	• Antibodies to expressed therapeutic protein	• Immunoadsorption/IgG cleaving enzyme for pre-existing AAV Abs • Rituximab/sirolimus for treatment emergent AAV Abs (and for transgene immunity?) • Complement inhibition
Cellular Immunity	• Cytotoxic T-cell, • Pre-existing immunity (memory T cells)?	• None	• CD8+ T cell responses targeting therapeutic protein	• Corticosteroids • Tolerance induction in liver directed gene therapy • Engineered TREG (“CAR Treg”)
Host Dependent Factors	• Concomitant infection/inflammation, HLA haplotype • Pre-existing immunity	• Expression of pattern recognition receptors (PRRs)	• Patients with null mutations (CRIM-negative) at increased risk	• No recent infection/vaccination • Immunomodulation in CRIM- negative patients (? tolerance induction) • Exclusion of patients with pre-existing immunity vs immuno-depletion/modulation
Vector Dependent Factors	• Vector dose • Route of administration • Vector purity • Empty capsid ratio	• CpG content • ITRs • Self-complementary vs single stranded	• Transgene product –vs untranslated product (e.g., shRNA, miRNA)	• Good manufacturing practices • Minimize empty capsid content in final product • Reduce CgG content of construct

Biodistribution

- Where in the body the virus (not transgene) migrates to (and persists)
- This is the “D” in ADME
- Often taken from preclinical animal studies
- Droplet digital PCR and qPCR are standard assays
- *EMA seems to imply that fewer tissues are required to be studied than FDA & IPRP

Long Term Follow-Up After Administration of Human Gene Therapy Products

Guidance for Industry

IPRP
International Pharmaceutical Regulators Programme

Expectations for Biodistribution (BD) Assessments for Gene Therapy (GT) Products

Approved by the IPRP Management Committee on 3 June 2018
12 April 2018

- **Luxturna** label contains organs where vector and transgene were detected <u>in animals</u> (NHP)

- **Zolgensma** label gives this information <u>in humans</u> (unfortunately one patient died and was given an autopsy to determine distribution—human data supersedes any animal data)

Shedding

- Shedding is the secretion of virus outside of the patient (saliva, nasal swab, tears, urine, feces, sweat)
  - The “E” in ADME (but is not a mass balance assessment)
  - Assessed periodically in trial similar to serum samples
  - Purpose is to assess risk to others, not study subject

LUXTURNA®
voretigene neparvovec-rzyl
for subretinal injection

- *LUXTURNA vector was shed transiently and at low levels in tears from the injected eye in 45% of the subjects in Study 2, and occasionally (7%) from the uninjected eye until Day 3 post-injection.*
- *Transient and low level shedding of LUXTURNA may occur in patient tears. Advise patients and/or their caregivers on proper handling of waste material generated from dressing, tears and nasal secretion, which may include storage of waste material in sealed bags prior to disposal. These handling precautions should be followed for up to 7 days following LUXTURNA administration.*

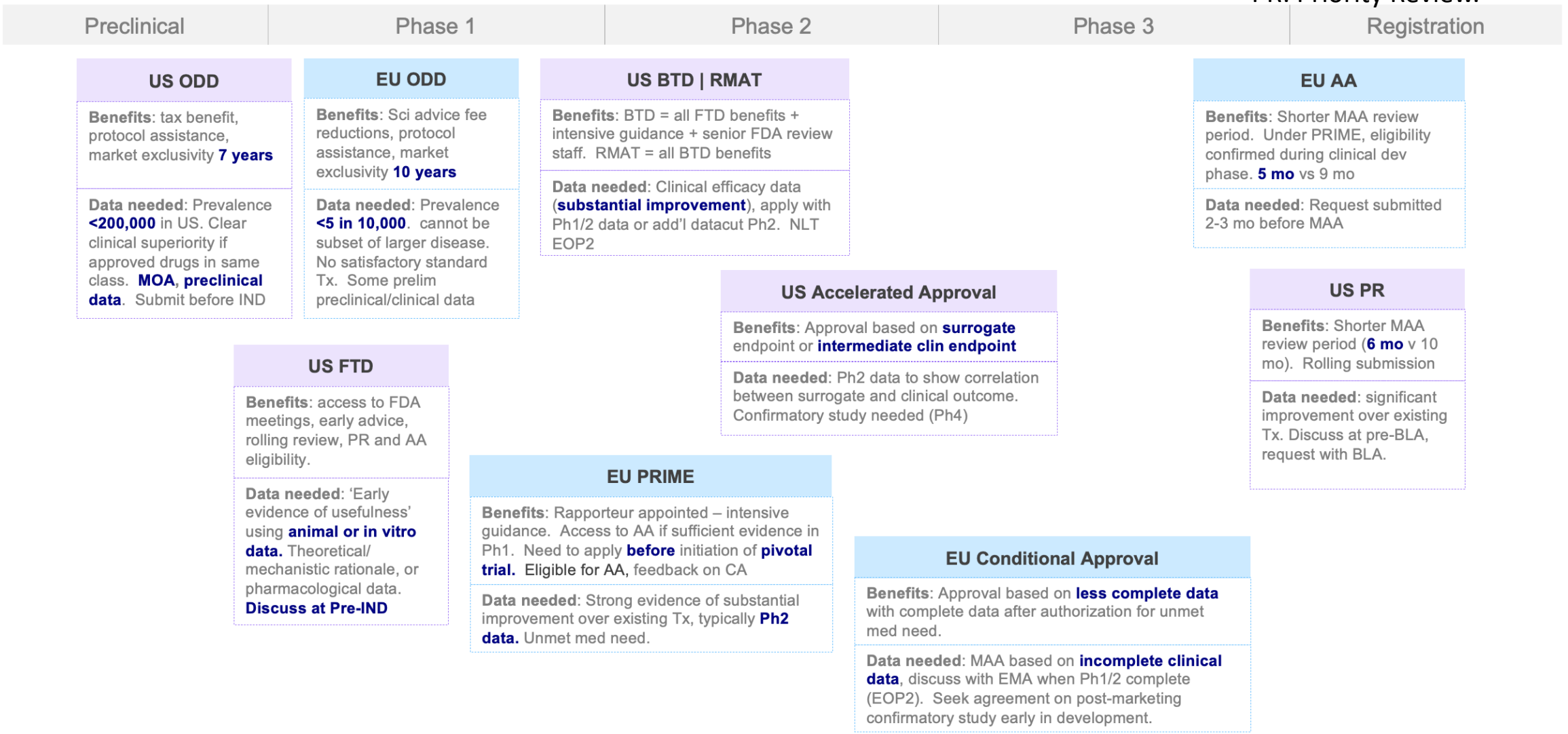
Design and Analysis of Shedding Studies for Virus or Bacteria-Based Gene Therapy and Oncolytic Products

Guidance for Industry

US and EU Regulatory Designations

(Each class has an associated data package)

ODD: Orphan Drug Designation;
BTD: Break- through Designation;
FTD: Fast Track Designation;
AA: Accelerated Assessment;
PR: Priority Review.



Huh, S., D'Souza, V., Balaji, A., & Fülle, H. J. *Regulatory Considerations in the Development of Gene Therapy Products*. In *Development of Gene Therapies* (pp. 313-338). Chapman and Hall/CRC.

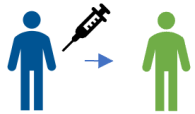
The Death of Jesse Gelsinger (1999)

Gelsinger was as a substitute for another volunteer who dropped out, despite having high ammonia levels that contraindicated by study inclusion/exclusion criteria.

UPenn failed to report that two patients had previously experienced serious side effects.

Informed-consent documentation did not disclose deaths of monkeys given a similar treatment.

Ethical Considerations

	Disease Specific Features			Features Specific to Gene Therapy					
	Rare	Severe	Pediatric	Irreversible	Potentially Harmful	Immunogenic	Lateral Transmission	Germline Transmission	Over Correction
									
Issue	**Patients to study drug response in a clinical trial may be limited; characterization of disease state itself may have scant information.**	**Disease under study may be severe, complicating the benefit-risk assessment.**	**Pediatric patients are particularly vulnerable, and studies in children usually require evidence of effectiveness in adults.**	**The ability to revise the dose for a patient is not possible with gene therapy. Information is limited in this respect due to usual rarity of the disease.**	**Intervention can have serious proximal and long-term health consequences.**	**Gene therapies may trigger immunologic memory, limiting ability to redose patients.**	**There is a theoretical risk to persons in contact with a patient administered a gene therapy.**	**Gene therapy may transduce gonads, leading to transgene transmission to offspring.**	**The use of gene therapy technology to alter populations for political/social ends is a possibility.**
Mitigation	Use of robust statistical designs to acquire as much information as possible and minimize patient exposure to investigational compound.	Quantitative benefit-risk assessments early in the drug development process, before patients have been dosed. Equipoise must be respected and continually re-evaluated.	Extra consideration to parental involvement in writing and reviewing the informed consent document.	Sponsors and health authorities need to continually monitor long-term effects, and revise the ICF to reflect the potentially long-term commitment between patient and treating physician. Maximizing trial efficiency during dose-finding.	Collaboration between sponsors, investigators, and health authorities in data sharing and long-term safety monitoring should become the norm. ICF must be transparent about potential for risk and benefit.	Efficient and statistically optimal trial designs should be evaluated by sponsors, reviewing health authorities, and the broader scientific community to identify opportunities for innovation	Health authority guidance should be followed in shedding studied; optimal statistical design could be applied in this setting to adjust patient monitoring.	Robust preclinical assessment of germline transmission risk must be conducted as part of a preclinical package. Risk could be disregarded if potential benefit to patient is sufficiently promising.	Gene therapy for the use of cosmetic or racial or behavioral changes should be outlawed, and sufficient penalty for overriding this guardrail should be put in place at the international level.

First Approved Gene Therapy—Lessons Learned

Alipogene tiparvovec (Glybera) was the first gene therapy approved in the European Union in 2012

Sponsor requested that the primary efficacy endpoint of triglyceride levels be changed to postprandial chylomicrons metabolism, and committed to a post-approval study of previously dosed patients to establish the validity of the new endpoint

This led to long-term funding commitments and in conjunction with manufacturing, regulatory, and access issues ultimately led to the drug's removal from the European market

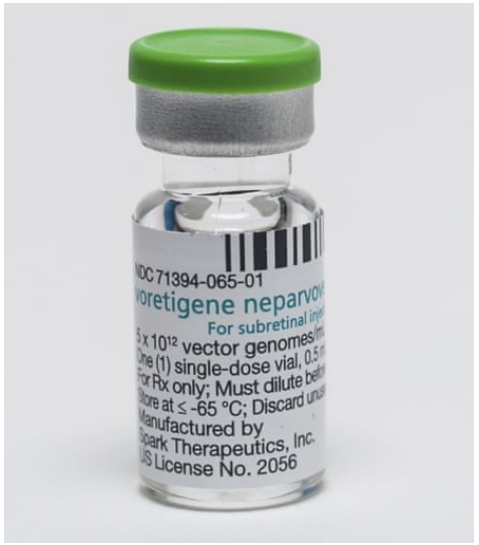
https://www.liebertpub.com/doi/10.1089/humc.2013.087

2017-2018: Gene Therapy's Big Year

LUXTURNA®
voretigene neparvovec-rzyl
for subretinal injection

KYMRIAH®
(tisagenlecleucel) Suspension for IV infusion

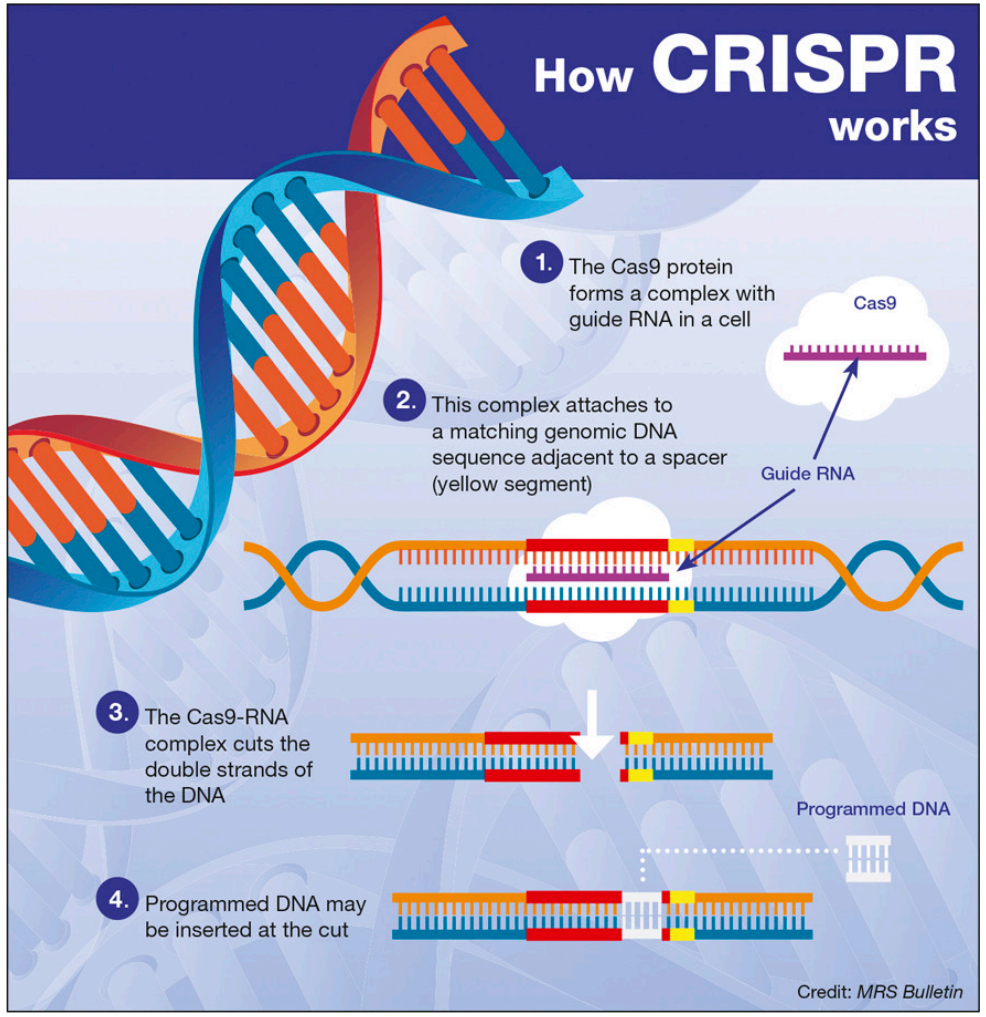
zolgensma®
(onasemnogene abeparvovec-xioi)
suspension for intravenous infusion



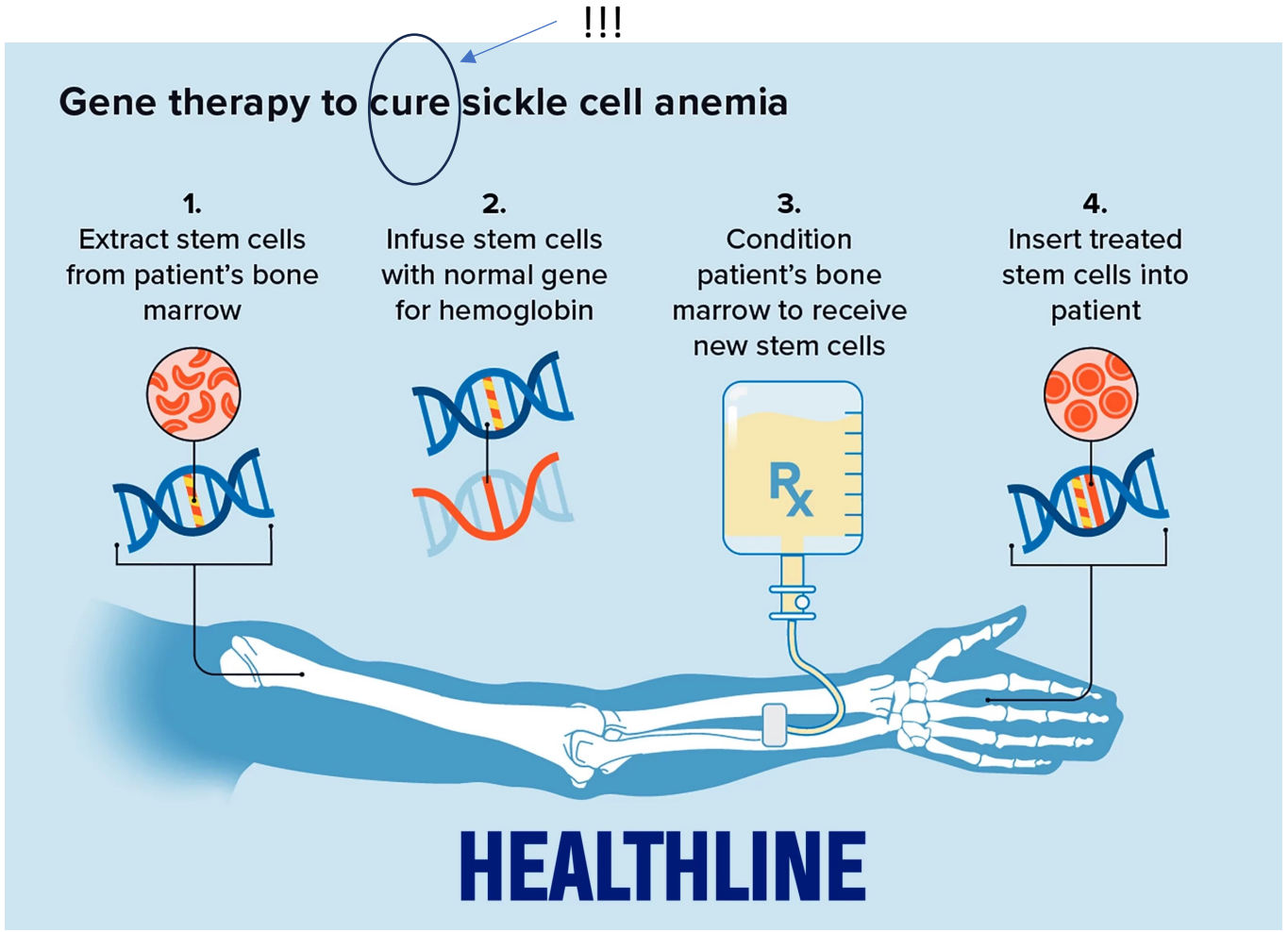
All drugs were approved with fewer than 100 patients dosed (!)

2023-4: Year of Gene Editing
(CRISPR--Clustered Regularly Interspaced Short Palindromic Repeats)

Casgevy and Lyfgenia applications received FDA designations: Priority Review, Orphan Drug, Fast Track and Regenerative Medicine Advanced Therapy designations



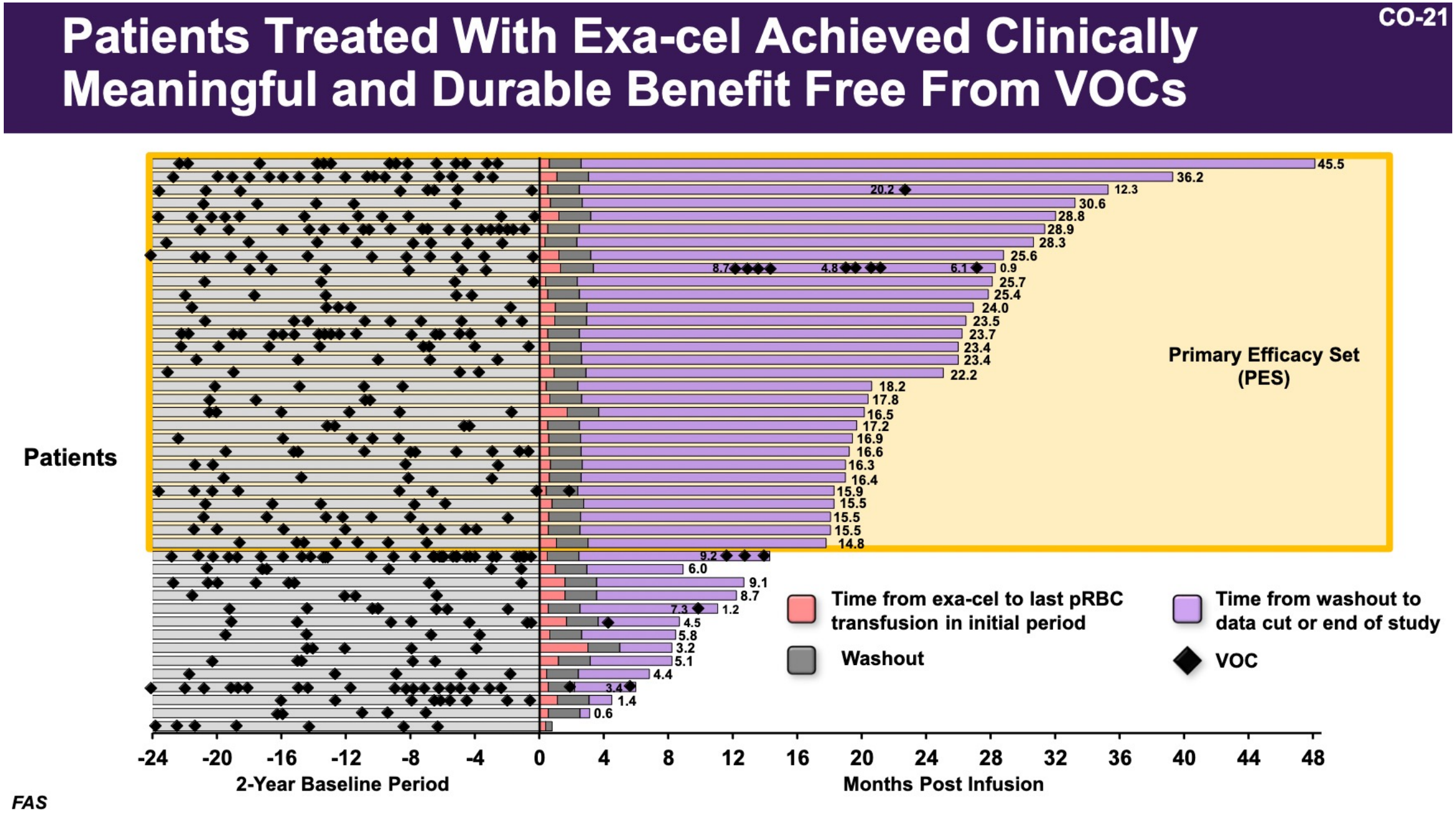
https://www.cambridge.org/core/journals/mrs-bulletin/news/crispr-implications-for-materials-science



https://pwonlyias.com/current-affairs/casgevy-therapy-a-gene-therapy-for-sickle-cell-disease/

Casgevy (exagamglogene autotemcel)

https://www.fda.gov/media/173472/download



Market Access, RWE, HEOR, and Commercial Models

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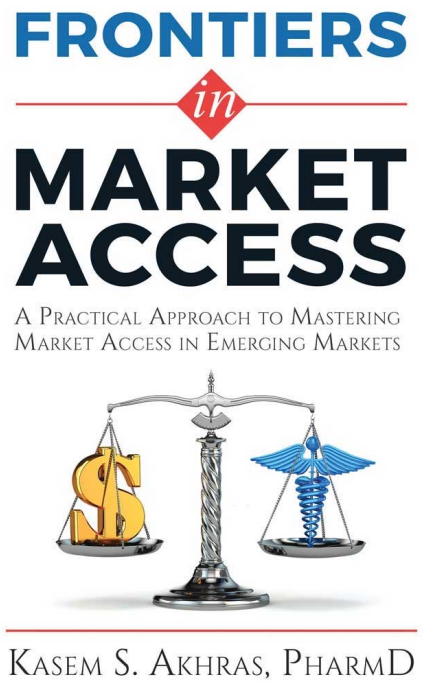
Commercial Models, Access Hurdles, and Health Economics of Gene Therapies

Kasem S. Akhras and Anish Patel



World's Most Expensive Drug Is Now $4.25 Million Gene Therapy

The one-time treatment, Lenmeldy, is used to correct the underlying cause of a hereditary condition called early-onset metachromatic leukodystrophy. *Photographer: Eric Piermont/AFP/ Getty Images*

By Gerry Smith

March 20, 2024 at 10:09 AM EDT

Clinical Development of Gene Therapies

- Preclinical and translational elements
- Clinical development plans
- 7 hallmarks of gene therapy trial design
- Clinical pharmacology principles
- Governance and evidence packages
- GTx in neurological indications
- Strategies for ultra-rare indications
- Areas in need of innovation
  - Dose finding
  - Platform trials
  - Adaptive endpoints
  - Innovation in long term follow-up

Chemistry, Manufacturing, and Controls (CMC)

12

Manufacturing, Analytical, and Process Comparability Challenges for Recombinant Adeno-Associated Virus (rAAV) Gene Therapy

Hannah K. Bare, Erik S. Barton, Aili Cheng, Brad Evans, Henry Gregory, Dan Griffin, William Kish, Rudra Mukherjee, Thomas Powers, Herbert A. Runnels, Daniel Ryan, Courtney D.K. Sloan, Austin Tritt, Ke Wang, Shun Zheng

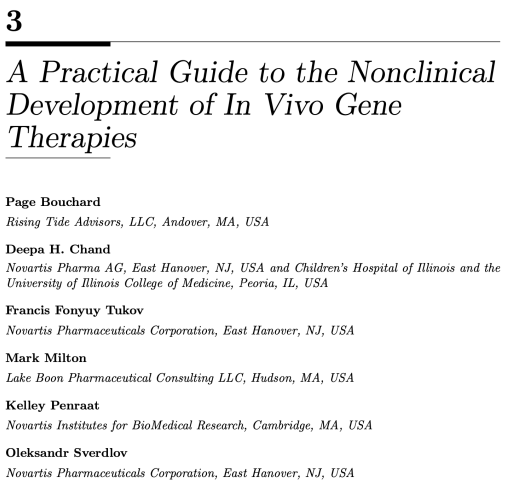
Biotherapeutic Technology Pharmaceutical Sciences, Pfizer

(Authors are listed in alphabetical order)

A summary of commonly used statistical methods for comparability assessment. SPI=Simultaneous Prediction Interval. BPI=Bayesian Prediction Interval. TOST=Two One-Sided Tests (*TOST includes both frequentist and Bayesian versions).

	SPI	**BPI**	**TOST***
Goal of the comparison	- Whole distribution/ range - Individual batch values matter - Assumes equal variance	- Whole distribution - Individual batch values matter	- Mean difference - Not individual batches - Does not have to assume equal variance
Benefit	- Easy to calculate and understand	- Relevant scientific knowledge is considered as one of the inputs	- Higher power to detect mean shift than the interval approaches
Limitation	- Lower power to detect mean shift when such a shift exists - Could get "too wide" and lose the purpose of serving as "tighter" limits if preferred sample size is not met	- Computation complexity (e.g., simulation-based results) - The choice of prior distributions needs to be justified scientifically by SME	- Challenging to set EAC based on safety and efficacy - Hard to power the test with proper sample size due to limited clinical need
Preferred sample size	- Larger pre-change n, but much smaller post-change n	- Larger pre-change n or small pre-change n with strong scientific prior knowledge	- Balanced and large sample size for both processes
Direction	- Directional: the old process is treated as the standard for the new process to fall within	- Directional: the old process is treated as the standard for the new process to fall within	- Non-directional: neither process is treated as standard (i.e., same "answer" regardless of the designation of pre- or post-change)

Preclinical and Translational Elements



3

A Practical Guide to the Nonclinical Development of In Vivo Gene Therapies

Page Bouchard
Rising Tide Advisors, LLC, Andover, MA, USA

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Goal: To identify efficacious and safe doses to support clinical trials

Some key questions and points to consider

- What is/are the intended clinical indication(s) and degree of target validation?
- What are the target tissues and cells for transduction?
- What are the logical/viable routes and methods for administration?
- What amount of transgene expression is required, where, and for how long?
- What are trans-species homology and comparative biology?
- Are there good/relevant animal models of the target disease?
- And More...

Types of studies

- Nonclinical PoC studies → to guide preclinical toxicology and early clinical trial design
  - Exploratory rodent biodistribution and safety study
  - Pilot rodent biodistribution and efficacy & safety study
  - Pivotal IND/BLA-enabling efficacy and safety study
- Nonclinical toxicology studies
  - Pilot (28-day, non-GLP) toxicity and biodistribution study
  - Pivotal (GLP-compliant) toxicity and biodistribution study
- Regulatory guidance on nonclinical safety and biodistribution assessment requirements is evolving
  - March 2023 → ICH S12; Nonclinical biodistribution considerations for gene therapy products

Translational Elements: Example in Amyotrophic Lateral Sclerosis

Table 1
The ALS Functional Rating Scale — Revised (ALSFRS-R)

1. Speech	
4	Normal speech processes
3	Detectable speech disturbance
2	Intelligible with repeating
1	Speech combined with nonvocal communication
0	Loss of useful speech
2. Salivation	
4	Normal
3	Slight but definite excess of saliva in mouth; may have nighttime drooling
2	Moderately excessive saliva; may have minimal drooling
1	Marked excess of saliva with some drooling
0	Marked drooling; requires constant tissue or handkerchief
3. Swallowing	
4	Normal eating habits
3	Early eating problems — occasional choking
2	Dietary consistency changes
1	Needs supplemental tube feeding
0	NPO (exclusively parenteral or enteral feeding)
4. Handwriting	
4	Normal
3	Slow or sloppy: all words are legible
2	Not all words are legible
1	Able to grip pen but unable to write
0	Unable to grip pen
5a. Cutting food and handling utensils (patients without gastrostomy)?	
4	Normal
3	Somewhat slow and clumsy, but no help needed
2	Can cut most foods, although clumsy and slow; some help needed
1	Food must be cut by someone, but can still feed slowly
0	Needs to be fed
5b. Cutting food and handling utensils (alternate scale for patients with gastrostomy)?	
4	Normal
3	Clumsy but able to perform all manipulations independently
2	Some help needed with closures and fasteners
1	Provides minimal assistance to caregiver
0	Unable to perform any aspect of task
6. Dressing and hygiene	
4	Normal function
3	Independent and complete self-care with effort or decreased efficiency
2	Intermittent assistance or substitute methods
1	Needs attendant for self-care
0	Total dependence
7. Turning in bed and adjusting bed clothes	
4	Normal
3	Somewhat slow and clumsy, but no help needed
2	Can turn alone or adjust sheets, but with great difficulty
1	Can initiate, but not turn or adjust sheets alone
0	Helpless
8. Walking	
4	Normal
3	Early ambulation difficulties
2	Walks with assistance
1	Nonambulatory functional movement
0	No purposeful leg movement
9. Climbing stairs	
4	Normal
3	Slow
2	Mild unsteadiness or fatigue
1	Needs assistance
0	Cannot do

Table 1. (*Continued*)

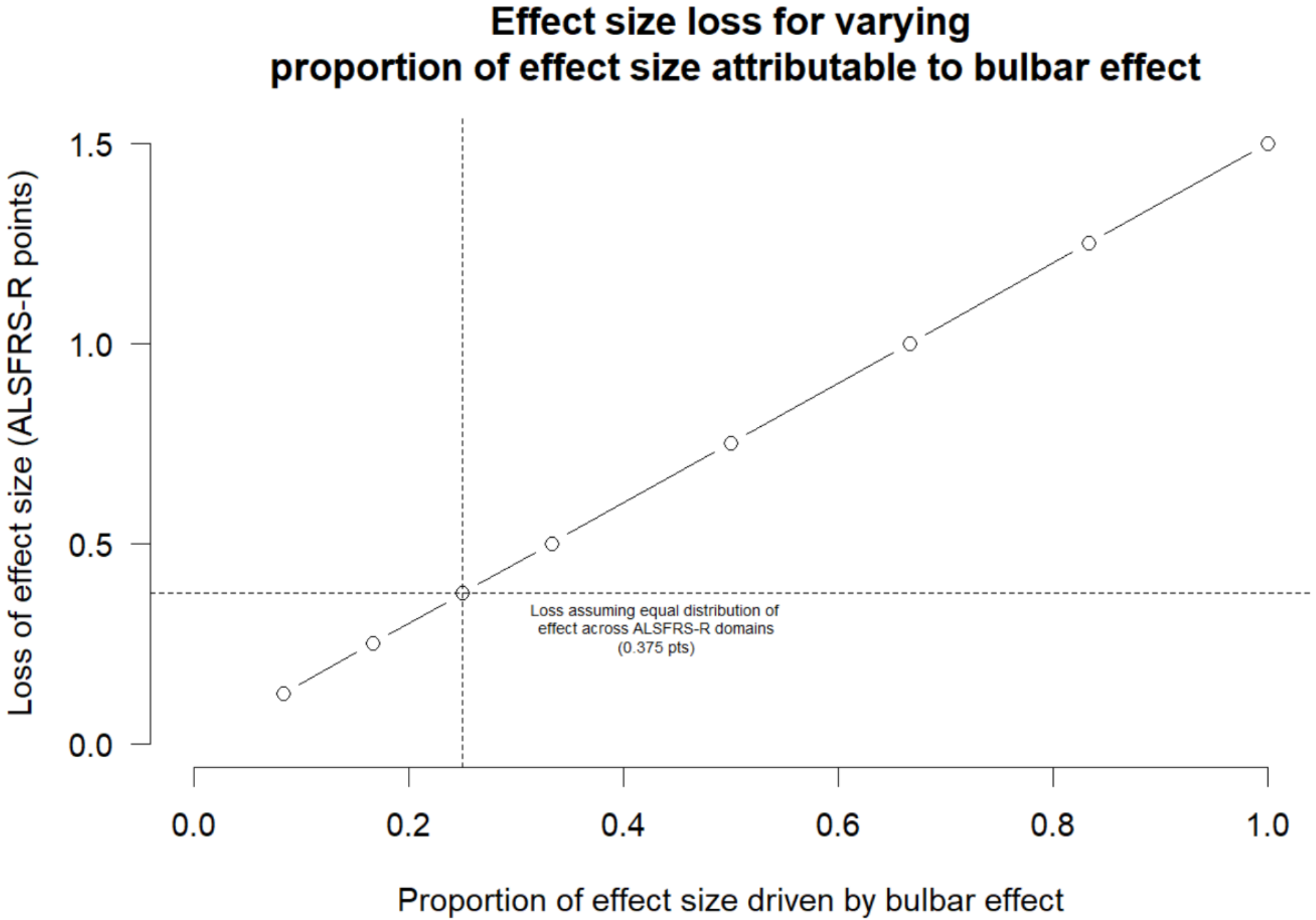
10. Dyspnea (new)	
4	None
3	Occurs when walking
2	Occurs with one or more of the following: eating, bathing, dressing (ADL)
1	Occurs at rest, difficulty breathing when either sitting or lying
0	Significant difficulty, considering using mechanical respiratory support
11. Orthopnea (new)	
4	None
3	Some difficulty sleeping at night due to shortness of breath, does not routinely use more than two pillows
2	Needs extra pillows in order to sleep (more than two)
1	Can only sleep sitting up
0	Unable to sleep
12. Respiratory insufficiency (new)	
4	None
3	Intermittent use of BiPAP
2	Continuous use of BiPAP during the night
1	Continuous use of BiPAP during the night and day
0	Invasive mechanical ventilation by intubation or tracheostomy

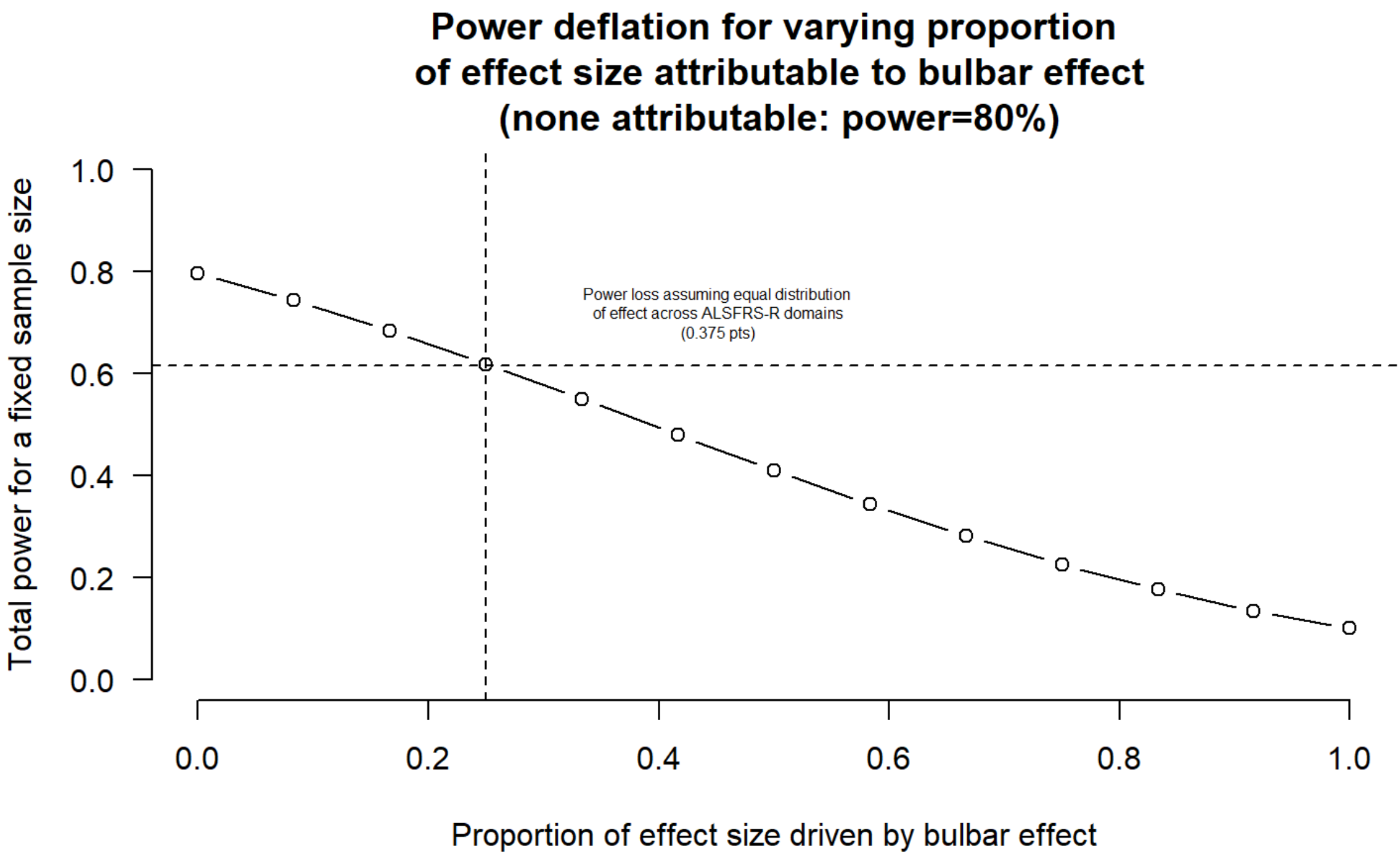
ALSFRS-R definitions

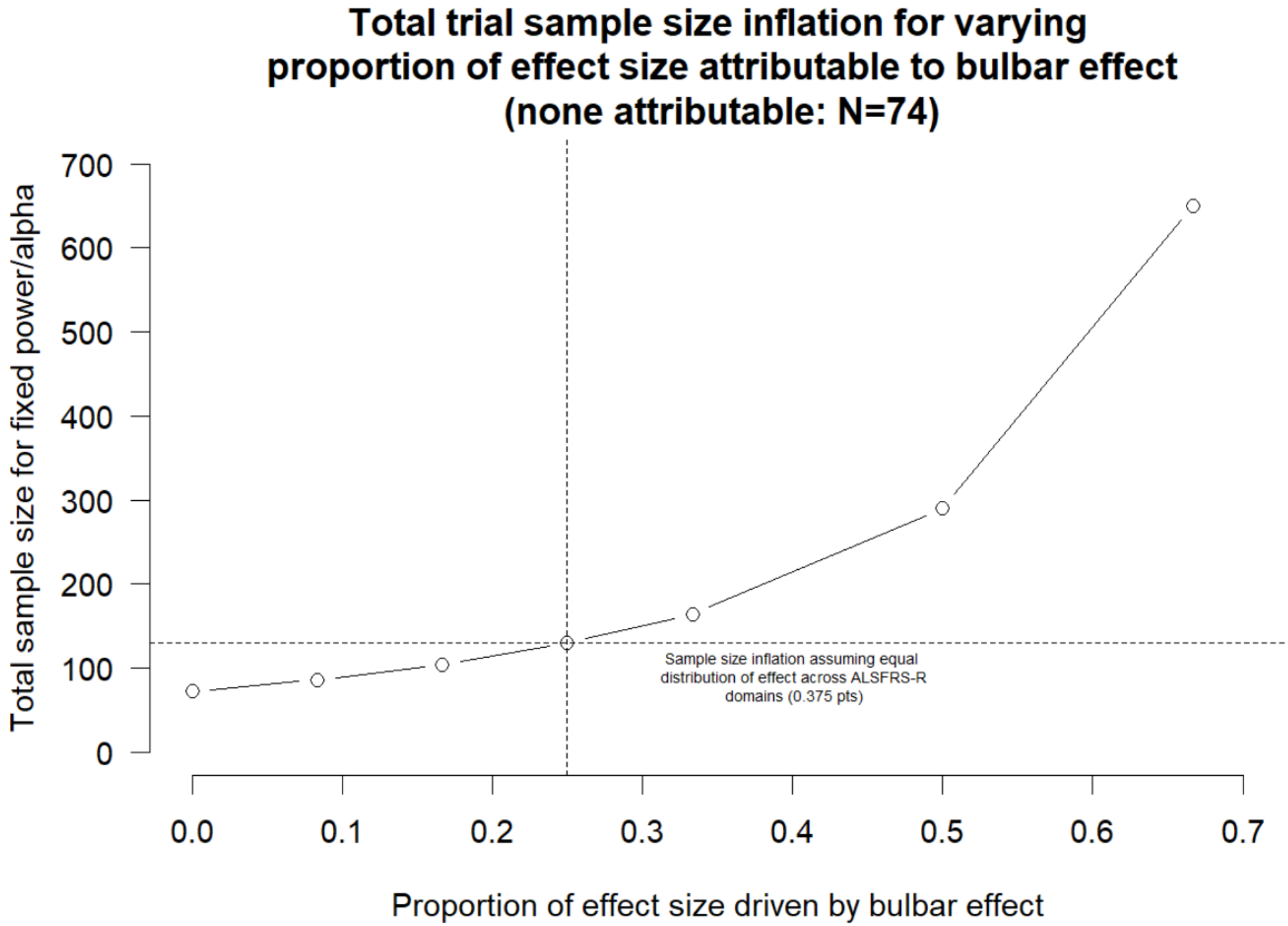
Cedarbaum et al 1999

ALSFRS-R items as a function of Lower Motor Neuron anatomy

ALSFRS-R Item	Functional Domain	Anatomic correlate/Key area to be transduced				
		Pons CN V & VII	Medulla CN IX, X, XII	Cervical Spinal Cord	Thoracic Spinal Cord	Lumbar Spinal Cord
1 Speech	Bulbar					
2 Salivation						
3 Swallowing						
4 Handwriting	Fine Motor					
5 Cutting food and handling utensils						
6 Dressing and hygiene						
7 Turning in bed and adjusting bedclothes	Gross Motor					
8 Walking						
9 Climbing stairs						
10 Dyspnea	Respiratory					
11 Orthopnea						
12 Respiratory insufficiency						

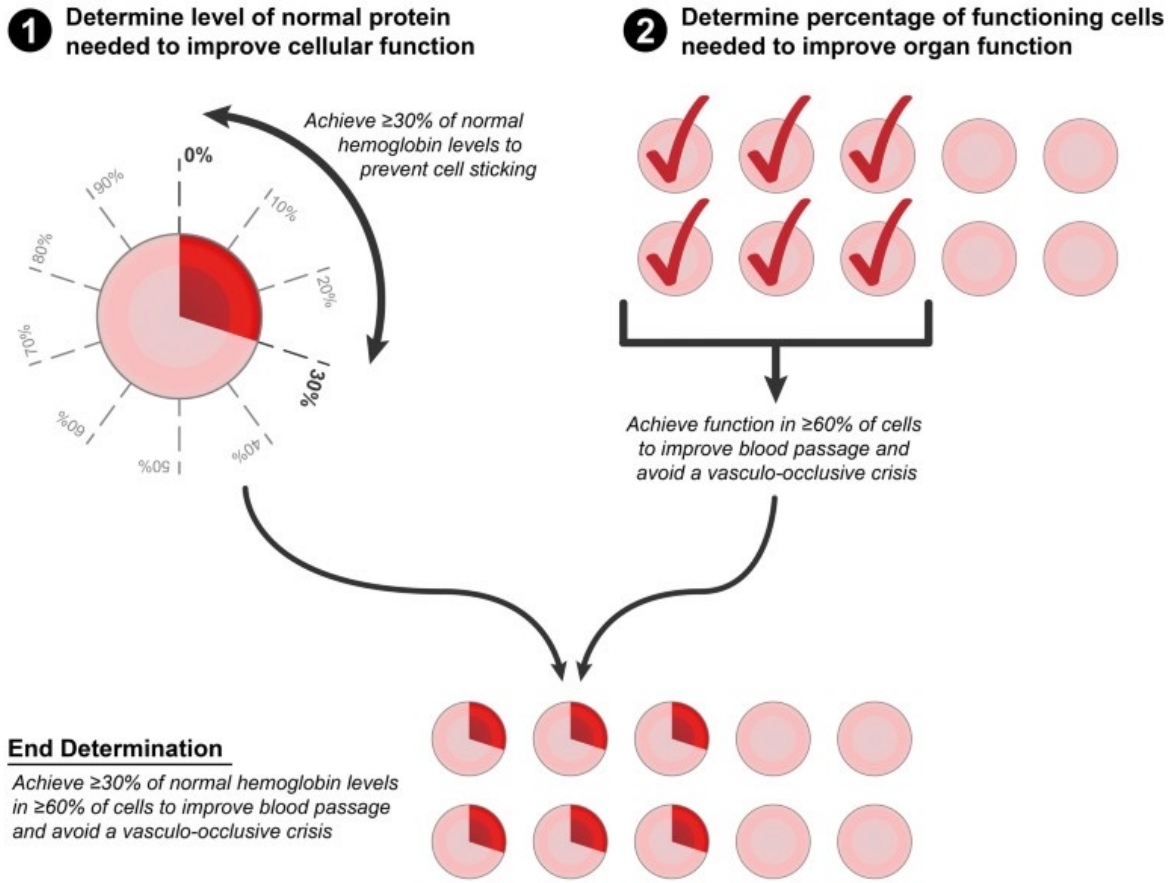

Effect size loss for varying
proportion of effect size attributable to bulbar effect
Loss of effect size (ALSFRS-R points)
1.5
1.0
0.5
0.0
Loss assuming equal distribution of
effect across ALSFRS-R domains
(0.375 pts)
0.0
0.2
0.4
0.6
0.8
1.0
Proportion of effect size driven by bulbar effect


Power deflation for varying proportion
of effect size attributable to bulbar effect
(none attributable: power=80%)
Power loss assuming equal distribution
of effect across ALSFRS-R domains
(0.375 pts)
Total power for a fixed sample size
1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.2
0.4
0.6
0.8
1.0
Proportion of effect size driven by bulbar effect


Total trial sample size inflation for varying proportion of effect size attributable to bulbar effect (none attributable: N=74)
Total sample size for fixed power/alpha
700
600
500
400
300
200
100
0
Sample size inflation assuming equal distribution of effect across ALSFRS-R domains (0.375 pts)
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
Proportion of effect size driven by bulbar effect

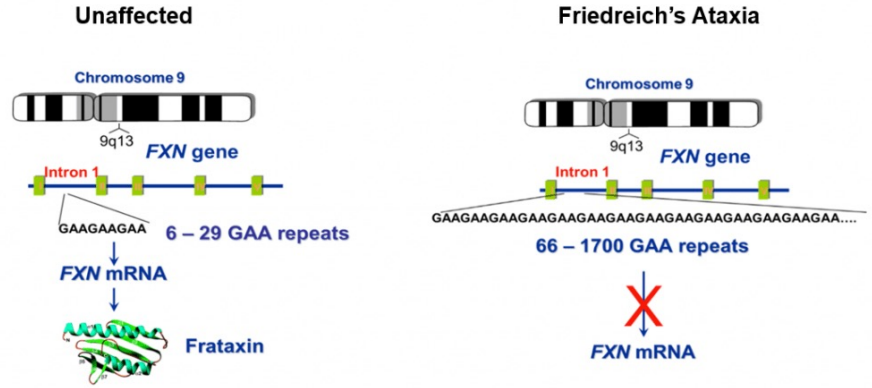
An Unspoken Need: Genetic Subpopulation Data

The Paradigm



https://www.nature.com/articles/d42473-018-00307-6

The Reality



https://sites.uab.edu/thenapieralalab/

Analysis Approaches to Identify Pharmacogenetic Associations With Pharmacodynamics

Daniel L. Hertz, Laura B. Ramsey, Mathangi Gopalakrishnan, J. Steven Leeder, Sara L. Van Driest

First published: 27 May 2021 | https://doi.org/10.1002/cpt.2312 | Citations: 2

Current and Next Steps Toward Prediction of Human Dose for Gene Therapy Using Translational Dose-Response Studies

Sergey Aksenov, John C. Roberts, Ganesh Mugundu, Karen Thudium Mueller, Indranil Bhattacharya, Michael A. Tortorici

First published: 08 August 2021 | https://doi.org/10.1002/cpt.2374 | Citations: 1

Linked article:: This article is linked to Rational clinical dose selection of adeno-associated virus-mediated gene therapy based on allometric principles, by Tang, F. *et al. Clin. Pharmacol. Ther.***110**, 803–807 (2021). https://doi.org/10.1002/cpt.2269.

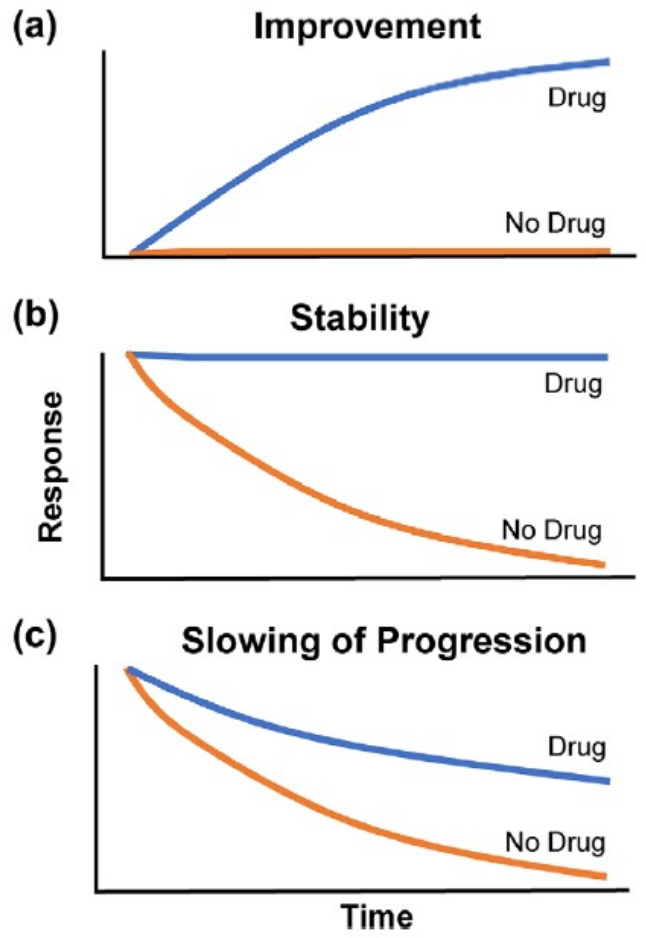
What kind of efficacy situation are we in?

(a) Improvement: likely not feasible with GTx in for neurodegenerative indication?

(b) Stability: what we are aiming for?

(c) Slowing of progression: this may be what we observe in the short term, due to onset of the drug (unknown), or in the long term (transduction is not enough)

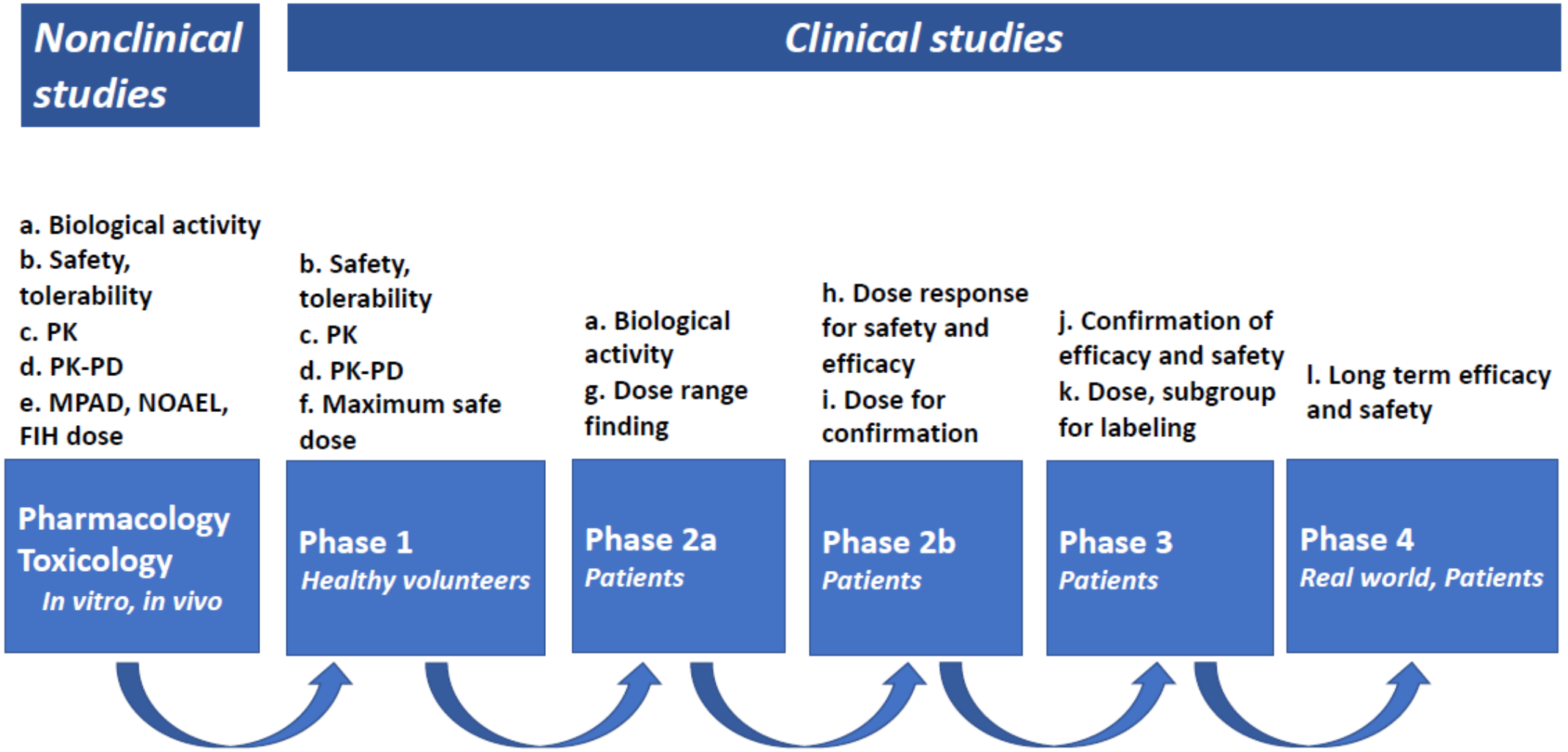
May need to also show improvement in QoL if in this situation



Cox, Gerald F. "The art and science of choosing efficacy endpoints for rare disease clinical trials." *American Journal of Medical Genetics Part A* 176.4 (2018): 759-772.

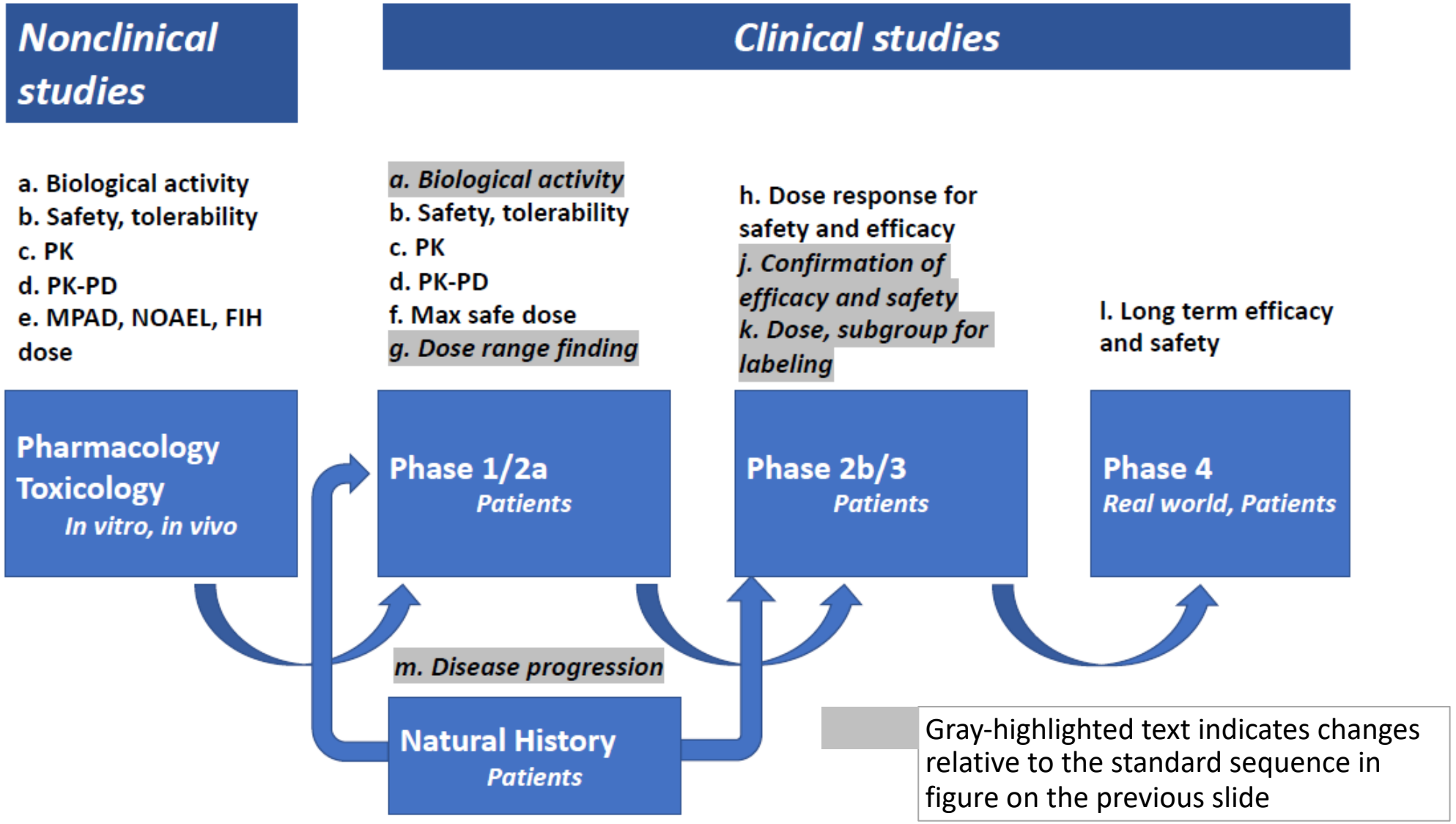
Clinical Development Plan for Traditional Pharmaceuticals 💊

(stepwise “learn & confirm”)



Oleksandr Sverdlov, Avery McIntosh, Jess LeClair, Sergey Aksenov. “Statistical Innovation for Gene Therapy Development: Clinical Trial Design and Analysis Considerations.” ISBN 9781032136554

CDP for Gene Therapies (more condensed, no HVs)



Oleksandr Sverdlov, Avery McIntosh, Jess LeClair, Sergey Aksenov. “Statistical Innovation for Gene Therapy Development: Clinical Trial Design and Analysis Considerations.” ISBN 9781032136554

Consequences of having only one pivotal trial in GTx indications

1. Dilution of effect size seen in Ph2 in later trials is a well-known phenomenon
   - Can be from underpowering (not enough subjects, **or** overestimated effect size)
2. Having a single pivotal trial in GTx risks overestimation of effect size
3. Health authorities, payers seem not to have recognized this phenomenon
   - As GTx continue to be approved, dilution effect can potentially limit business proposition
4. The statistician can contribute to a strong submission and access package by being involved from the near start of a clinical program, understanding the scientific and pharmacological basis for efficacy, and educating stakeholders on how to create a robust drug package

$$P(False\ Positive \mid Reject\ H_o) = \frac{P(Reject\ H_o \cap False\ Positive)}{P(Reject\ H_0)} = \frac{\alpha}{\alpha + 1 - \beta}$$

The Role of *p*-Values in Judging the Strength of Evidence and Realistic Replication Expectations

Eric W. Gibson

Clinical Development and Analytics, Novartis Pharmaceuticals, East Hanover, NJ

ABSTRACT

p-Values are viewed by many as the root cause of the so-called replication crisis, which is characterized by the prevalence of positive scientific findings that are contradicted in subsequent studies. The spectrum of proposed solutions includes redefining statistical significance, abandoning the concept of statistical significance, or eliminating the use of *p*-values altogether. The unintended consequence of these proposals has been confusion within the scientific community, especially in the absence of consensus or clear alternatives. The goal of this article is to reframe the perceived replication crisis. I argue that this crisis is to a large extent the result of excessive optimism based on unknowingly (and sometimes knowingly) overstated evidence. As a remedy, I suggest a four-part guide to navigating statistical inference with *p*-values that is accessible for scientists. Examples taken from pharmaceutical drug development for heart failure illustrate key concepts.

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DOI: 10.1177/1745691614551642
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SAGE

Beyond Power Calculations: Assessing Type S (Sign) and Type M (Magnitude) Errors

Andrew Gelman[1] and John Carlin[2,3]
[1]Department of Statistics and Department of Political Science, Columbia University; [2]Clinical Epidemiology and Biostatistics Unit, Murdoch Children's Research Institute, Parkville, Victoria, Australia; and [3]Department of Paediatrics and School of Population and Global Health, University of Melbourne

Abstract

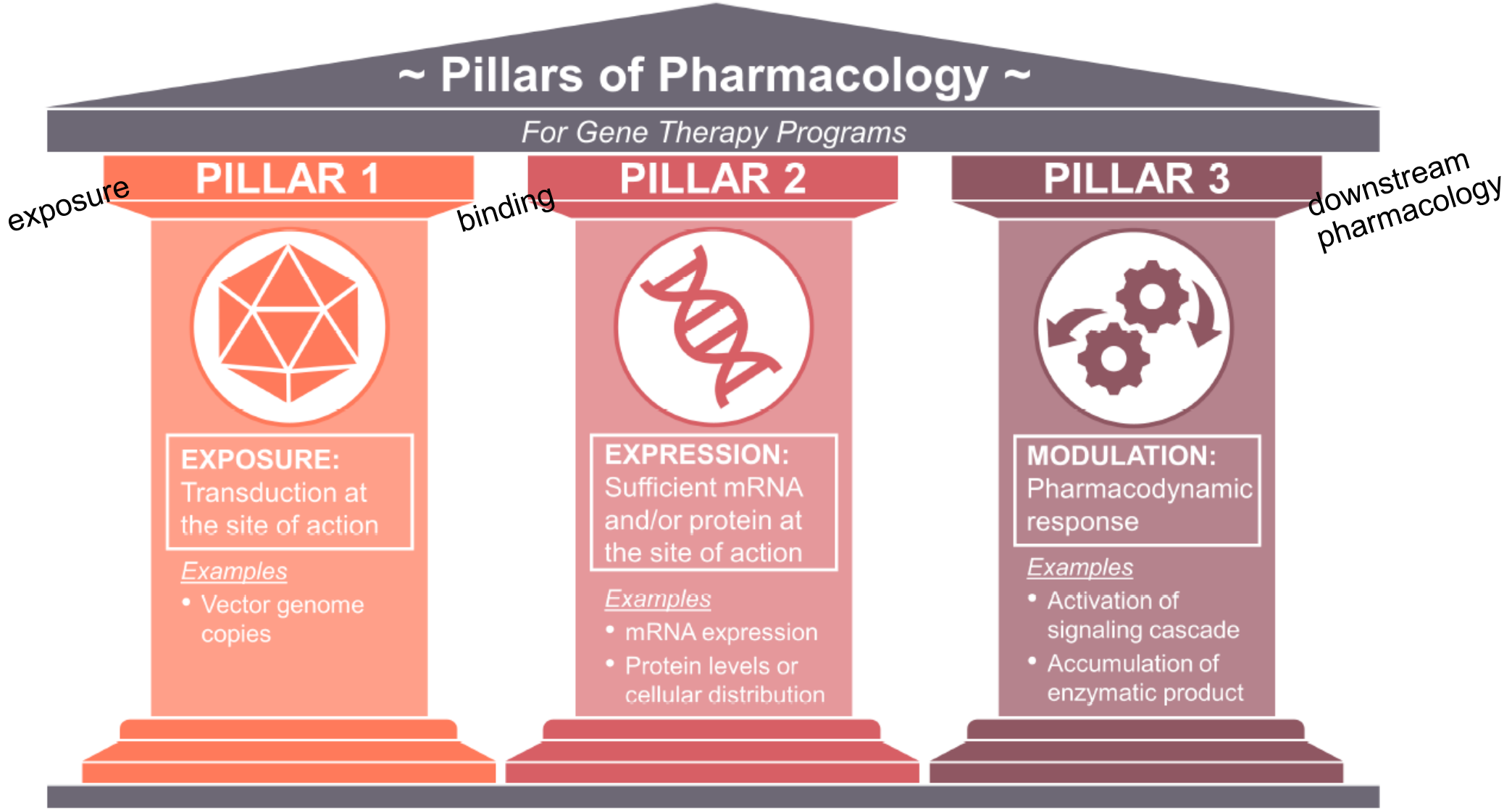
Statistical power analysis provides the conventional approach to assess error rates when designing a research study. However, power analysis is flawed in that a narrow emphasis on statistical significance is placed as the primary focus of study design. In noisy, small-sample settings, statistically significant results can often be misleading. To help researchers address this problem in the context of their own studies, we recommend design calculations in which (a) the probability of an estimate being in the wrong direction (*Type S [sign] error*) and (b) the factor by which the magnitude of an effect might be overestimated (*Type M [magnitude] error* or *exaggeration ratio*) are estimated. We illustrate with examples from recent published research and discuss the largest challenge in a design calculation: coming up with reasonable estimates of plausible effect sizes based on external information.

Seven Hallmarks of Gene Therapy Trial Design

1. Disease modifying (curative??)
2. Usually rare disease
3. 1x administration
4. No consensus on what endpoint measures pharmacologic activity
5. Challenging safety monitoring
6. May be challenging to dose placebo in a trial
7. Long-term safety and efficacy difficult to predict

Oleksandr Sverdlov, Avery McIntosh, Jess LeClair, Sergey Aksenov. “Statistical Innovation for Gene Therapy Development: Clinical Trial Design and Analysis Considerations.” ISBN 9781032136554

Defining Success by Pharmacology Principles



Mohamed Hassanein, Kelly A Fader, David Beidler. "Biomarkers in Gene Therapy Development for Rare Diseases." ISBN 9781032136554

Sponsor Governance

The normal framework of pre-specifying success criteria at each stage should be relaxed for sponsor governance purposes in some cases

Neuro indications will often have multiple imaging, digital, functional, fluid biomarker scales

Not always clear which should be used to indicate PD activity or clinical efficacy

Post-hoc testing of multiple endpoints can be hugely informative (win ratio, MDRI, Claggett method, Wei-Lachin multivariate one-sided test, etc.)

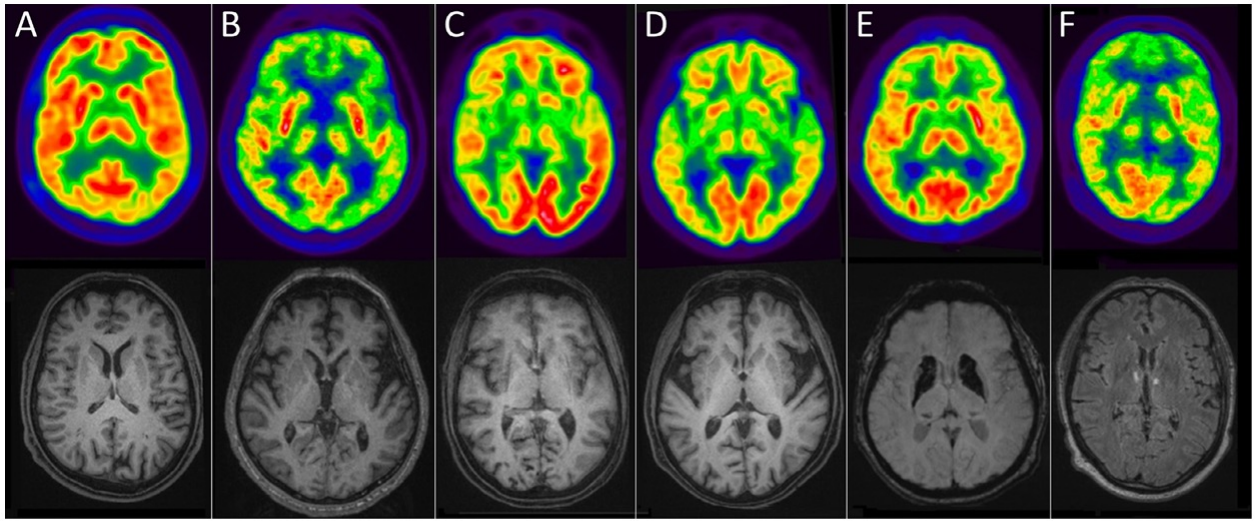


Figure 2 A number of ^{18}F-FDG PET/MR cases showing striatal hypometabolism (upper row) in different conditions. (A) healthy control (to be used as reference), (B) progressive supranuclear palsy, (C) multiple system atrophy with predominant parkinsonism, (D) Huntington disease, (E) FAHR's disease and (F) thalamic bilateral lacunar infarct. On the lower row corresponding anatomic images: T1 isotropic MPRAGE (A-D), Susceptibility-Weighted Imaging (SWI) (E) and T2-Flair (F).

Cecchin et al.
https://doi.org/10.1053/j.semnuclmed.2021.03.003

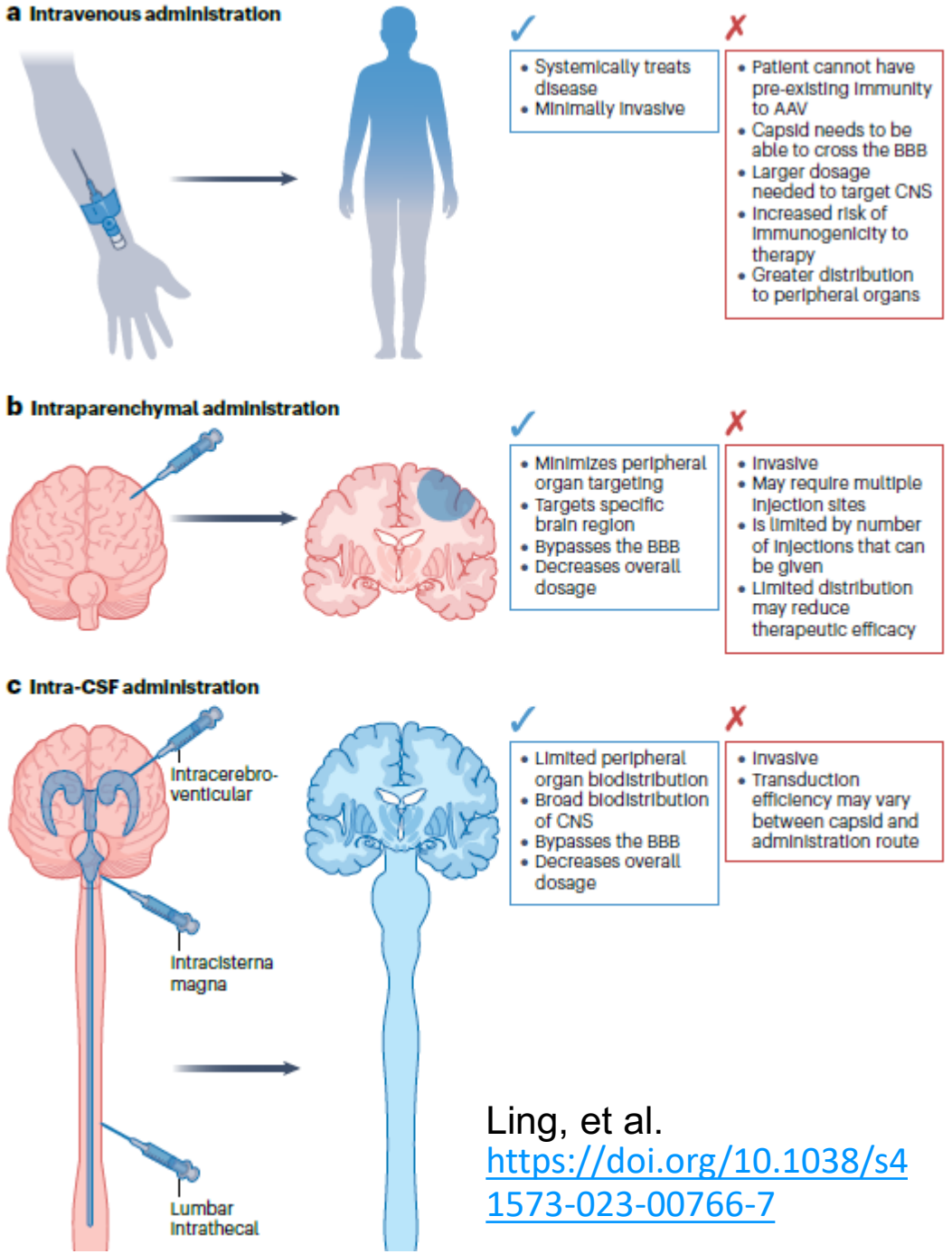
Gene Therapy for Neurological Diseases

Potential of a GTx intervention is most apparent for diseases of the CNS

Neurons are terminally differentiated, in contrast to the constantly dividing cells found in other organ systems

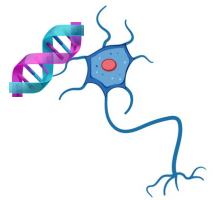
Thus, protein expression from an episomal gene cannot be diluted by cell division in CNS

Potentially more favorable safety profile (fewer vectors pass through liver vs systemic admin.)



Ling, et al.
https://doi.org/10.1038/s41573-023-00766-7

Challenges in GTx for Neurological Indications



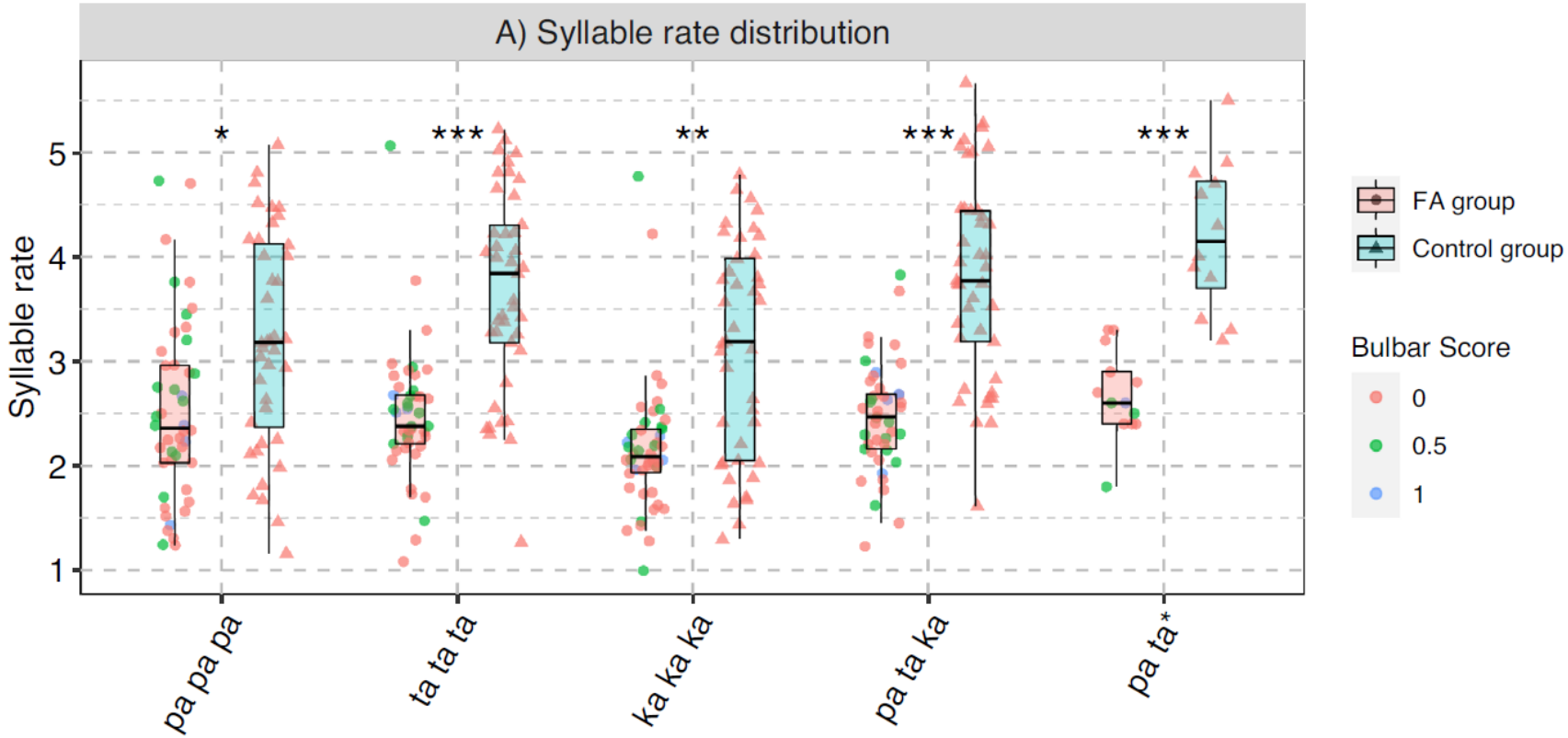
- For many CNS indications, understanding the pharmacodynamic effect will be challenging
- Reasons
  - lack of access to target tissue (invasive, hard to measure biomarkers or target engagement);
  - lack of understanding of pathogenesis (e.g. which cells/ tissues are implicated);
  - lack of validated biomarkers of pharmacodynamic effect (if the drug *is* working, may only know from functional or cognitive scales)
- This all makes *decision making* in this area very challenging. How do we know a drug works?

Tools for Neuro-muscular, -cognitive GTx

Digital Endpoints

- Actigraphy
- High freq cognitive testing

Using Natural History to link neuro-cog and fluid / imaging biomarkers



Mueller, et al. https://doi.org/10.1002/acn3.51438

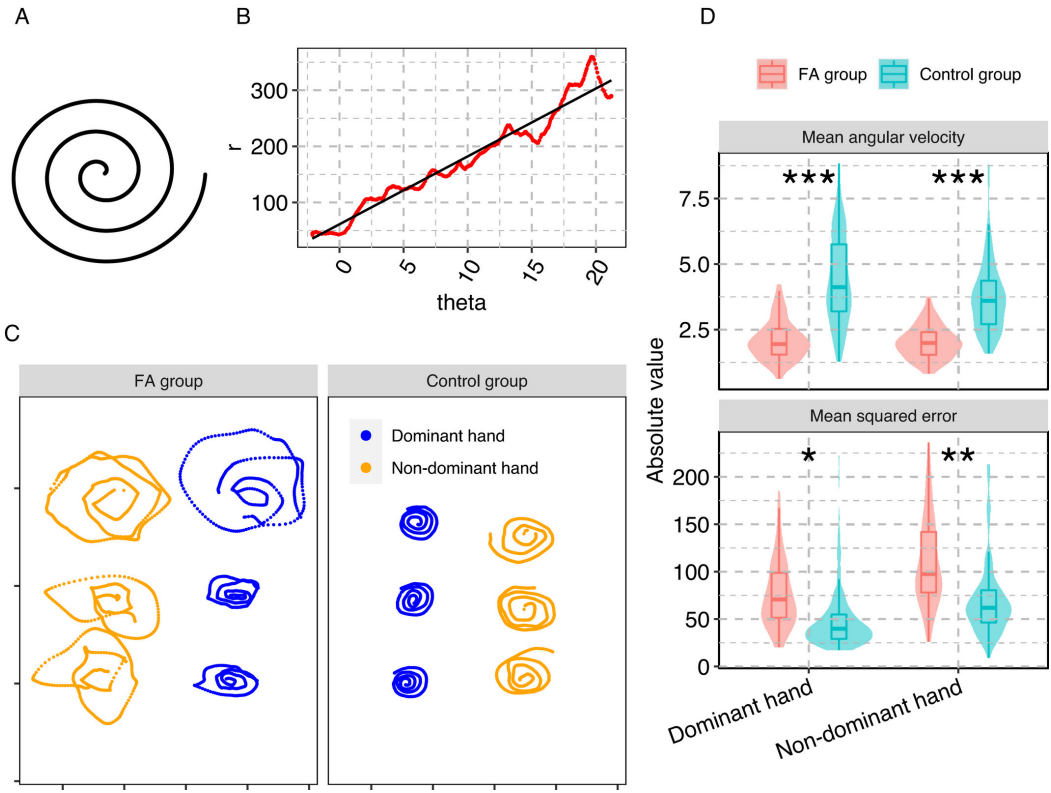
John Shoffner [Astellas], “The Future of in vivo rAAV Gene Therapies for Rare Neurological Diseases.” ISBN 9781032136554

Digital Endpoints for Clinical Studies

ANNALS of Clinical and Translational Neurology
Open Access
AMERICAN NEUROLOGICAL ASSOCIATION
Research Article | Open Access

Digital endpoints for self-administered home-based functional assessment in pediatric Friedreich's ataxia

Arne Mueller, Elaine Paterson, Avery McIntosh, Jens Praestgaard, Mary Bylo, Holger Hoefling



- Four questions we can ask of a digital metric:

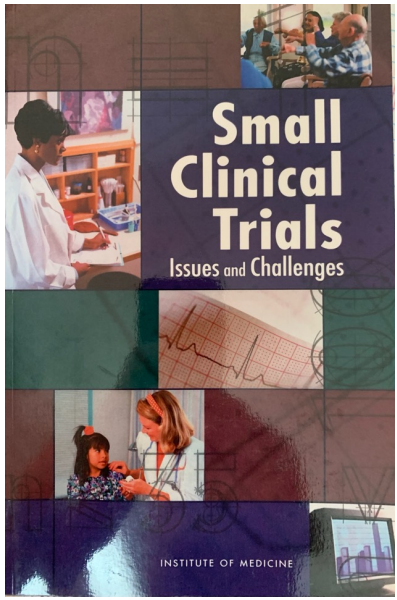
1. Are digital measures feasible and can high-quality data be collected in the home setting with the device?
2. Can digital measures differentiate patients from non-affected, and measure progression in patients?
3. How do these digital endpoints correlate with, or predict, the gold standard outcome measure?
4. How does the detectable effect size for these digital measures compare with the effect size measured with the gold standard?

Recommendations for Clinical Development of Neuro GTx

1. Utilization of patient registries and natural history studies to identify subjects.
2. Collaboration with patient advocacy groups to create educational materials providing high-quality information on gene therapy.
3. Implementation of adaptive/flexible trial designs to reduce study durations and cohort size (Bothwell et al., 2018).
4. Leverage surrogate endpoints that are reasonably likely to predict clinical benefit.
5. Adoption of decentralized clinical trial solutions (e.g., telehealth visits, electronic collection of adverse event data, home visits via visiting nurse) to help reduce the patient burden of participating in trials.
6. Inclusion of endpoints related to health economics to preemptively address payer concerns and build a solid rationale for reimbursement.
7. Utilization of real-world data to monitor safety and efficacy over extended time periods.

Petra Kaufmann [Vigil], Amanda Haidet-Phillips [Sarepta]. “Bringing Gene Therapy to Patients: A Clinical Development Perspective Based on Brain and Neuromuscular Diseases.” ISBN 9781032136554

Summary of US Institutes of Medicine Committee's Recommendations from the summit and publication on Small Clinical Trial



(2001)

- Define the research question.
  - Before undertaking a small clinical trial it is particularly important that the research question be well defined and that the outcomes and conditions to be evaluated be selected in a manner that will most likely help clinicians make therapeutic decisions.
- Tailor the design.
  - Careful consideration of alternative statistical design and analysis methods should occur at all stages in the multistep process of planning a clinical trial. When designing a small clinical trial, it is particularly important that statistical design and analysis methods be customized to address the clinical research question and study population.
- Clarify the methods of reporting the results of clinical trials.
  - In reporting the results of a small clinical trial, with its inherent limitations, it is particularly important to carefully describe all sample characteristics and methods of data collection and analysis for synthesis of the data from research.
- Perform corroborative statistical analyses.
  - Given the greater uncertainties inherent in small clinical trials, several alternative statistical analyses should be performed to evaluate the consistency and robustness of the results of a small clinical trial.
- Exercise caution in interpretation.
  - One should exercise caution in the interpretation of the results of small clinical trials before attempting to extrapolate or generalize those results.
- More research on alternative designs is needed.
  - Appropriate federal agencies should increase support for expanded theoretical and empirical research on the performances of alternative study designs and analysis methods that can be applied to small studies. ...

Some Design Options for *Ultra*-Rare Diseases

- Randomized? Controlled? Single-arm?
  - RCT likely not ethical or feasible in a trial with ~10-15 patients
- Delayed-start /
  - Compare patients who get drug at time x vs those initially randomized to sham/pbo
- **Baseline-controlled trial (before-and-after)**
  - For single-arm studies
  - Drawback: how can we ensure estimates are not biased due to Hawthorne effect, investigator/caregiver bias?
  - If we have a robust biomarker of target engagement, this could cut it
- **Decision Analysis-Based design**
  - Utility assigned to side-effects & treatment effects (between 0-1). Combines probability of event * utility. Solicit expert opinion on prob. and utility in planning stages, then perform sensitivity analysis to vary these estimates across ranges
  - May be useful as supportive analysis to argue for BLA. Seems far out for primary efficacy endpoint
- **Ranking and Selection design**
  - Rank GTx vs sham in order of preference (most useful for many possible options). Can construct an “ethical cost” function that considers severity of inferior treatments
  - I actually think this method has a lot of promise under the circumstances. Drawback: neither I, nor I imagine FDA have any experience with this paradigm
- **Sequential trial**
  - Enroll subjects 1 at a time and ask statistical hypothesis question to either accept or reject null hypothesis
  - Drawback: have to wait to defined endpoint for each patient before making a decision: stop, or enroll more. Does not allow controlling for important baseline prognostic variables
- Crossover trials, N-of-1 trials, Randomized withdrawal, Early escape
  - Not applicable to GTx due to 1x administration
- Risk-based (“assured”) allocation
  - Allow individuals at greater risk to be randomized to drug
  - Drawback: complex analysis, more severe disease may be refractory to any treatment
- Adaptive randomization (“play the winner”)
  - Drawback: requires fast readout on efficacy per person to change the allocation. Not optimal in slow progressing disease

Should we dose escalate with such a limited number of patients?

- Like most of our other programs, dose escalation is complicated by the small patient population, only more so for ultra-rare programs
- Ethical concerns include: if a patient is underdosed, they may be forever ineligible for the final decided MTD ***or*** any other drug using an AAV vector
- Overdose during escalation could give permanent overexpression toxicity, or potentially severe shorter-term complications (liver, hepatocytes, etc.)
- A very strong dose translation methodology will have to be employed:
  - What assumptions do we have
  - Are murine models similar enough (e.g. in some diseases the mouse models are hemizygous knockout males, while the target for investigational drug population is heterozygous—does this have implications for the therapeutic window?)
  - Do we feel confident we can go forward with a single middle-of-the-road dose level?

Methods of analysis: what is appropriate under these uniquely constrained circumstances?

- Do we have to adhere to a probabilistic framework? (e.g. “normal” frequentist statistics, Bayesian statistics)
- What about other methods?
  - E.g. utility-based or ethical : may be optimal from a health economics/ public health standpoint

Methods of analysis: Predicted individual treatment effect (PITE)

- See Rosenkranz 2020
- Used as a decision framework for exploratory subgroups

Methods of analysis: Bayesian methods (& meta-analysis)

- Enables us to ask more meaningful questions of the data
  - "What is the probability that our treatment effect is >δ ?" rather than:
  - "What is the probability if we had no drug effect we'd see a statistic at least as extreme as what we saw?"

- Not often used in pivotal studies (but this is changing…)
- Very useful to incorporate subject-matter opinion, or previously generated data
  - Not so useful in an ultra-rare disease
- Key question: will FDA let us use these methods in a primary or supportive fashion? (I personally feel we should press hard on this point—these methods could be pivotal to making statements such as: "there is a 95% chance that change from baseline is >0, and >50% chance it is past our MCID")

Methods of analysis: Longitudinal models

- Very useful to track longitudinal change in individuals (MMRM, mixed-model repeated measures)
- Uses more data than a single cross-sectional measurement
- If it's single-arm, how to we make sure the endpoint is not biased due to Hawthorne effect or physician/caregiver bias? If it's an objective physical biomarker this will help
  - Although even "hard" physiological endpoints have been observed to change under caregivers (heart rate, etc)

Methods of analysis: selection (ranking) trial

- Selection designs are designed to make a prioritization between promising “experimental” regimens when there is no a priori data to prefer one regimen over the other.
- In this design, patients are randomized to two or more “competing” regimens/agents. The final results are then ranked, and the arm with the best observed outcome is selected for further study. The sample size requirements for this design are based on providing a high probability of choosing the best arm as long as the expected outcome in that arm exceeds any other arm by a clinically meaningful margin (e.g., at least 15%). This design does not provide answers concerning the relative merits of similar regimens because it does not test the null hypothesis of equality. This design approach was used by Lustberg et al. to make a selection between two doses of Mitomycin C followed by irinotecan in patients with advanced esophageal and gastroesophageal junction adenocarcinomas. The trial used a two-stage Simon design with individual decision rules for efficacy for each experimental arm with α and β of 0.1. The final results from the two arms were ranked to make a recommendation that the low-dose arm was both well tolerated and efficacious.

- Simon R, Wittes RE, Ellenberg SE. Randomized phase II clinical trials. Cancer Treat Rep 1985;69:1375–1381. [PubMed: 4075313]

Methods of analysis: multi-domain responder index (MDRI)

- Used when symptoms are heterogeneous across domains (behavior, structural, functional, cognitive), not within a given domain
  - Mepsevii (vestronidase alfa) from Ultragenyx for MPS VII (Sly syndrome)
  - Aldurazyme (laronidase) for MPS I, from Biomarin (supportive)
  - Elosulfase alfa (Vimazim) for MPS IV from Biomarin (supportive)

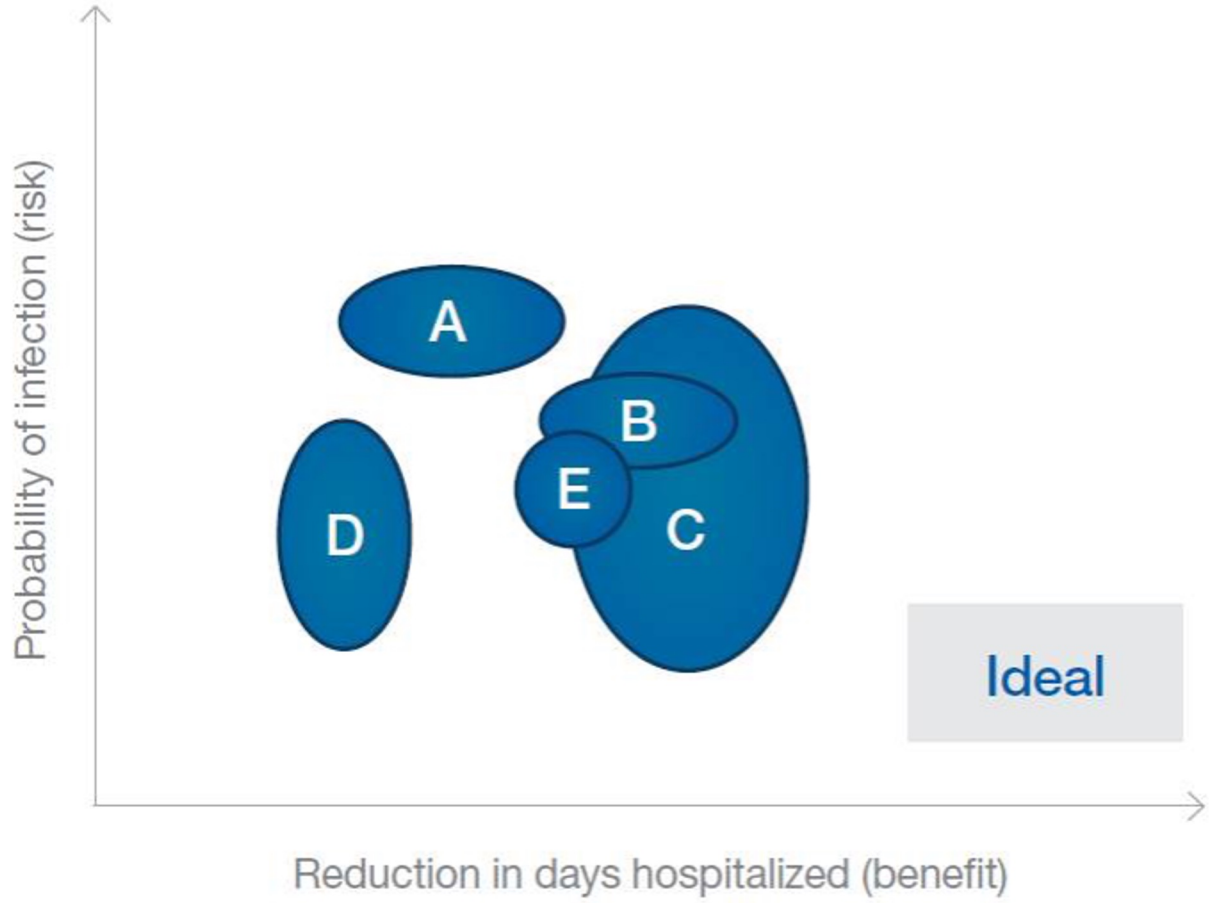
  Requires understanding what is a meaningful clinical change in each domain (how likely is this in an ultra-rare setting?)

Methods of analysis: MANCOVA

- “Multivariate analysis of covariance (MANCOVA) is an extension of analysis of covariance (ANCOVA) methods to cover cases where there is **more than one dependent variable** and where the control of concomitant continuous independent variables – covariates – is required. The most prominent benefit of the MANCOVA design over the simple MANOVA is the 'factoring out' of noise or error that has been introduced by the covariant.”
- ANOVA and all variants have as a requirement “normality” (bell-shaped distribution) of data, which is guaranteed in probability for means as $n \rightarrow \infty$, but for very small sample sizes will inflate Type I (false positive) error

Methods of analysis: patient-centered benefit-risk

- Selection of therapy based on patient (or caregiver) assessment of tradeoffs of benefits and risks
- A framework for decision making under uncertainty that accounts for patient preference
- https://mdic.org/resource/patient-centered-benefit-risk-pcbr-framework/#download_form

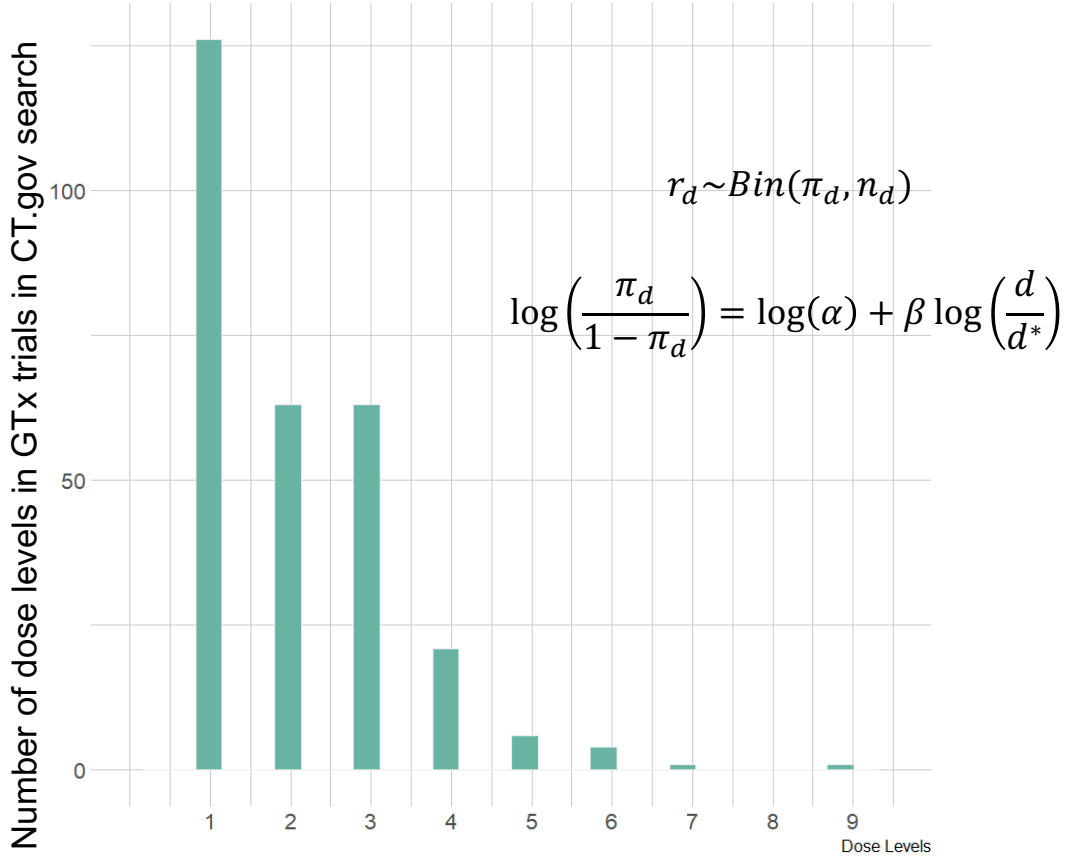


Example Areas for Innovation/ Adaptivity

(Trial & CDP level)

1. **Quantitative dose finding** ***(paper in preparation)***
2. Vectors /ph1 platform trial (TBD)
3. **Adaptive endpoints (nusinersen)**
4. **Platform trials for long term follow-up** ***(published)***

1

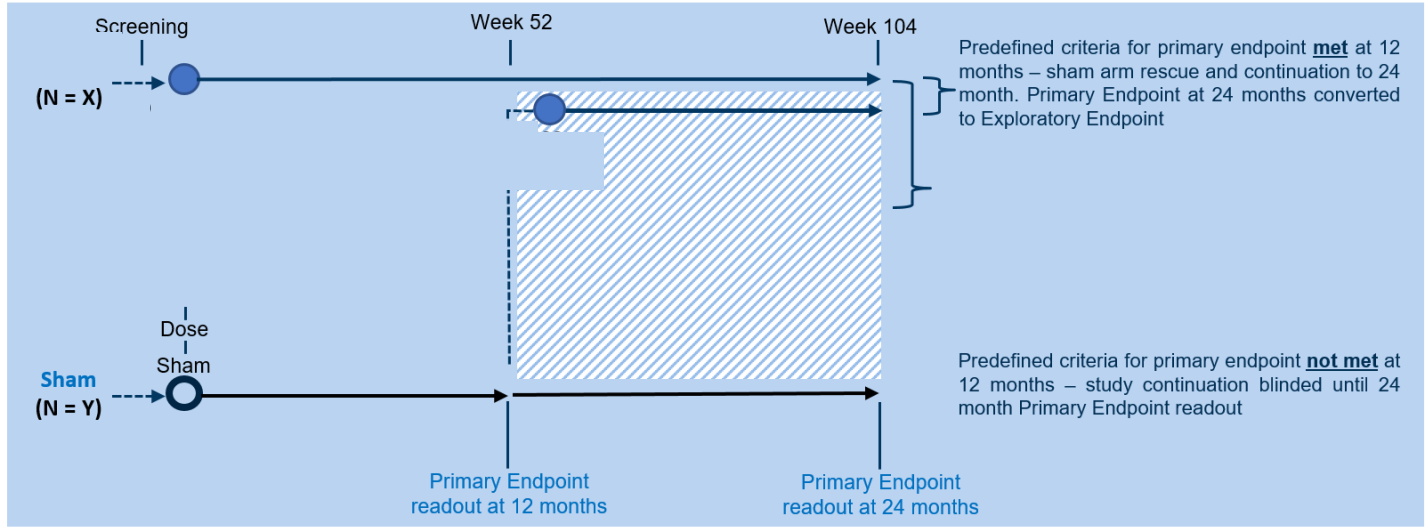


2

Studying Multiple Versions of a Cellular or Gene Therapy Product in an Early-Phase Clinical Trial

Guidance for Industry

3



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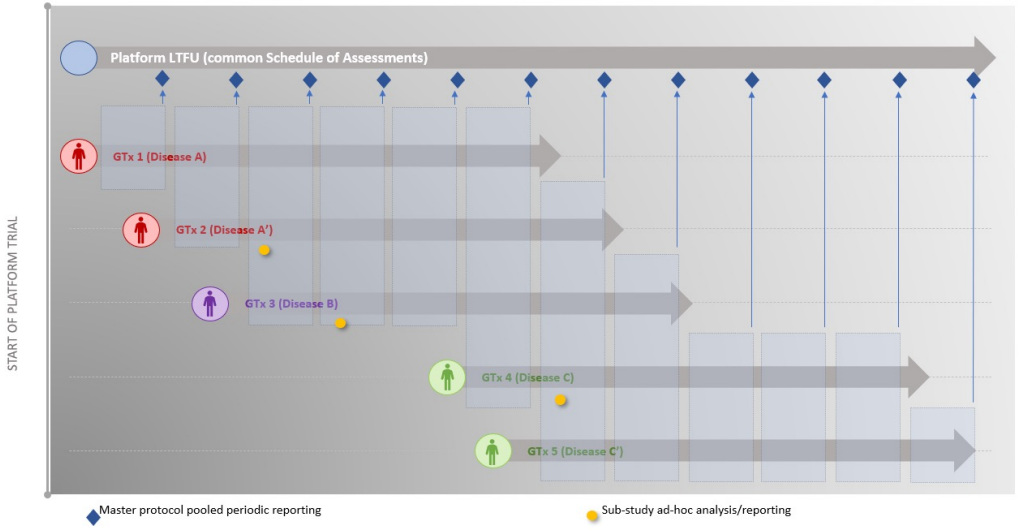


Dose Finding (outside of gene therapies)

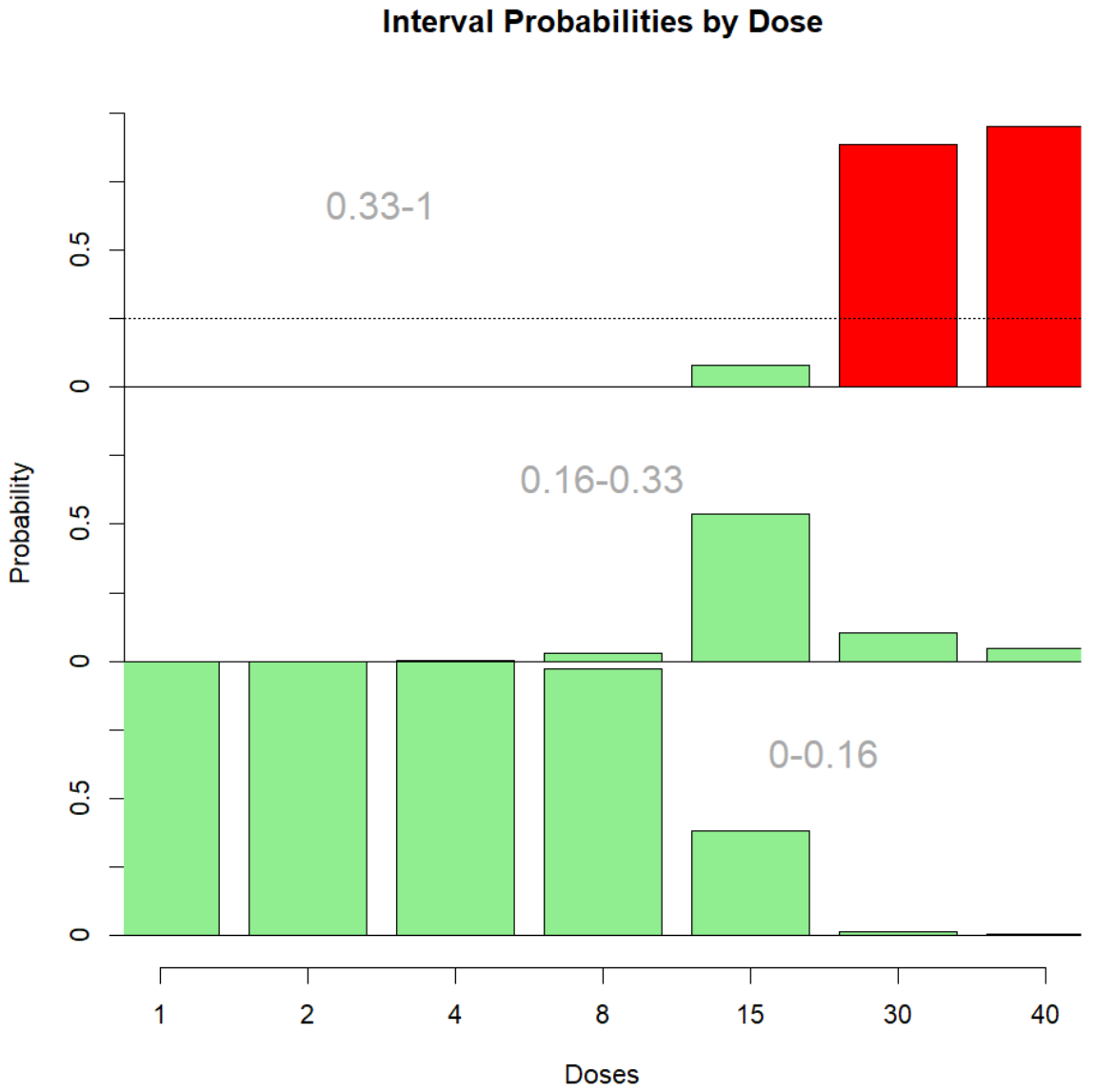
One popular method in oncology dose-finding Ph1 trials is BLRM

Bayesian Logistic Regression Model

$$r_d \sim Bin(\pi_d, n_d)$$

$$\log\left(\frac{\pi_d}{1-\pi_d}\right) = \log(\alpha) + \beta \log\left(\frac{d}{d^*}\right)$$

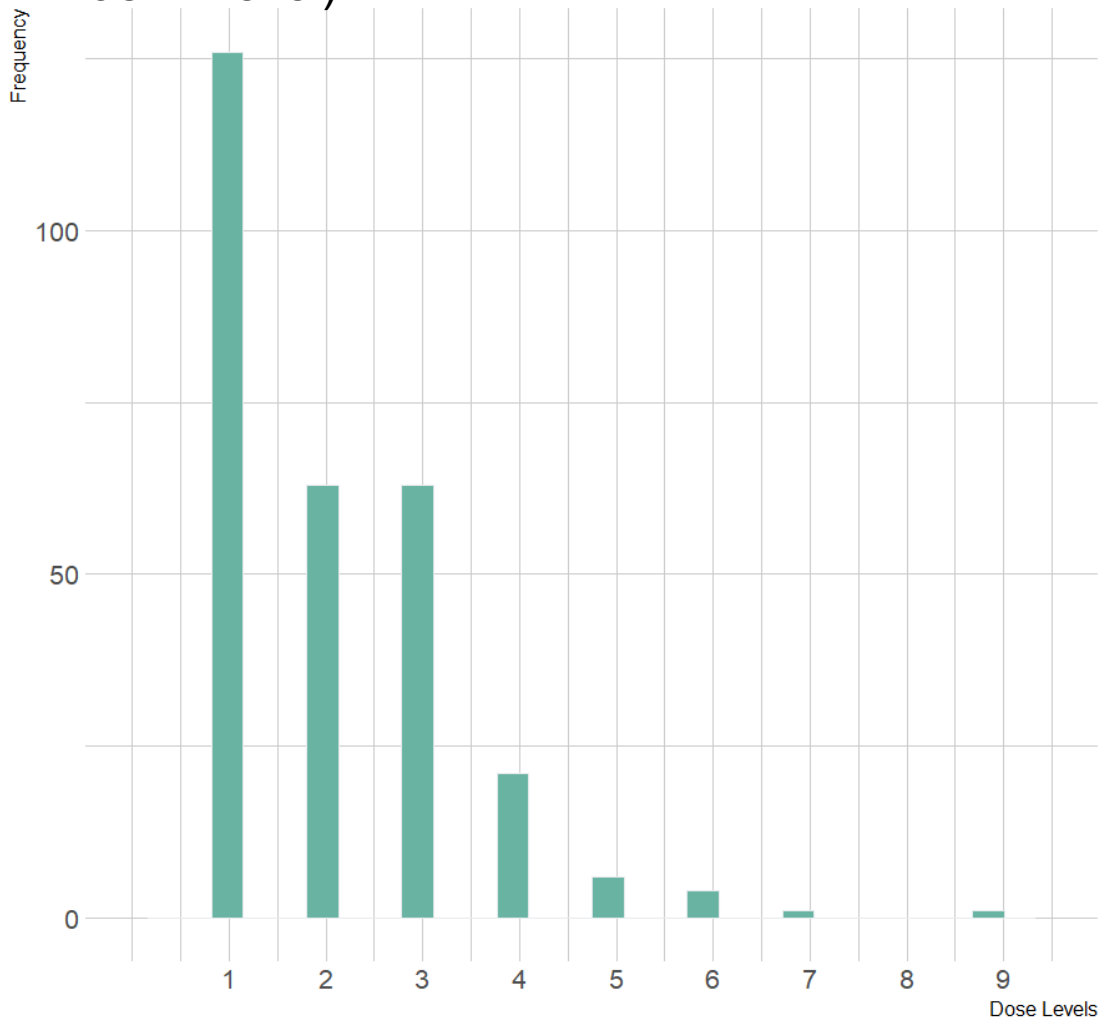
with $(\beta > 0), r_d =$ observed dose limiting toxicity, $\pi_d =$ true rate at dose level *d*, $n_d =$ number of subjects in dose cohort *d*, and d^* = a reference dose level



Typical distribution of Dose Levels in Early Phase GTx Trials

	Maximum dose levels	Max (non-oncology indications)	Max (oncology indications)
1 dose level	126	91	35
2 dose levels	63	56	7
3 dose levels	63	49	14
4 dose levels	21	14	7
5 dose levels	6	5	1
6 dose levels	4	3	1
7 dose levels	1	1	0
8 dose levels	0	0	0
9 dose levels	1	0	1
Unspecified (but implied >1)	49	21	28

ClinicalTrials.gov search found 334 GTx Ph1 trials with completion dates after 2020. Median number of dose levels was 2, but many had an unspecified number of dose levels (but the implication was it was >1 level)



Issues with Quantitative Dose Finding in GTx

1. Gene therapies can only be dosed 1x due to immunogenicity, and subjects are forgoing any future re-dose or even any other (possibly superior) AAV therapy—the benefit/risk is just a different situation from oncology, also the diseases are often severe but perhaps the patients are not facing imminent death like in an oncology trial

   Often in oncology an accelerated titration type design is used to quickly get to the therapeutic range. GTx will likely not have that possibility

2. Small # dose levels usually (in this situation, BLRM becomes highly dependent on the prior)

3. Small # patients per dose level usually (makes it a sharp tipping point, almost like 3+3, also heavily dependent on prior specification)

4. Prior elicitation is challenging if no previous human data—need to describe when it's ok to borrow from a similar program and when not (e.g. with novel engineered capsids/new delivery mechanisms, this is not appropriate)

5. There are two classes of DLTs (transient and "permanent," so a single endpoint for a DLT may not capture the clinical complexity)

Simulations for Dose-finding using BLRM

- Determine whether correct dose chosen
- 3 Dose cohorts varying cohort size (N=3, 4, 5)
- Combinations of AESI and DLT rates
- EWOC considerations for AESIs and DLTs: 0.5 and 0.2, respectively
- Dose chosen is highest dose where both EWOC conditions are satisfied
- Prior Distribution: MVN ($\mathbf{0,\Sigma}$) where $\mathbf{\Sigma =}$ ($\sigma^2 = 2$, 0, $\sigma^2 = 1$)

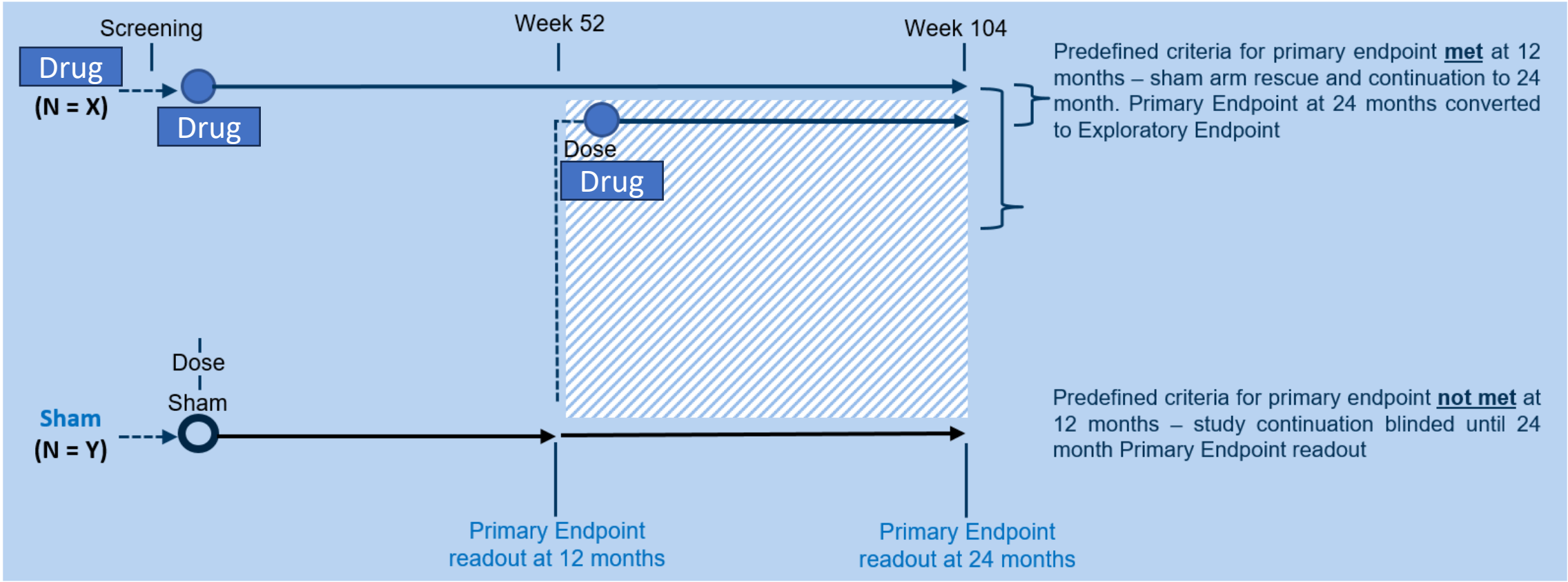
Simulations for Dose-finding using BLRM

- Combinations of AESI and DLT rates

Results pending

Scenario/ DLT rates for 2/3 dose levels	Resolvable class	Non-resolvable class
Safe for both	(0, 10, 10)	(0, 0, 10)
Safe for non-resolvable	(0, 30, 50)	(0, 0, 10)
Mixed for both	(0, 20, 40)	(0, 20, 30)
Unsafe for both	(20, 50, 70)	(20, 20, 50)
Safe for resolvable, unsafe for non-resolvable (least likely)	(0, 10, 10)	(20, 20, 50)

Clinical design has to balance ethical imperative to rescue if effective with lack of understanding of drug onset



Long Term Follow-Up (LTFU) for Gene Therapy

Why do GTx trials need long term follow-up?

- The long term safety profile of GTx products is still uncertain
- Long term data is required to fully assess benefit-risk profile
- Want to quantify the length of efficacy: 5,10 years? Lifetime?
- Assess adverse events due to the vectors:
  - Viral reactivation, immune reactions, off-target effects (e.g., dorsal root ganglion damage)
  - Risk of cancer from activating oncogenes if there is integration into the genome
  - Off-target edits from gene editing
- Collect data on long term biodistribution and viral shedding

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Challenges

- FDA / EMA require sponsors to enroll patients administered a GTx product into LTFU study
- 5 – 15 years of follow-up
- Unprecedented length of engagement w/ patients: risk of loss to follow-up and lack of protocol adherence

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Innovative solutions

- Platform trials / Master protocols
- Robust Bayesian hierarchical models (EXNEX) for borrowing safety information across gene therapy modalities
- Time-to-event models for adverse events
- Using existing patient registries
- Decentralized trials and use of electronic devices for data capture

Health Authority Guidances: LTFU

- Potential risks from integration activity of vector/genome editing
  - Insertional mutagenesis
  - Consequences from prolonged expression
  - Latency (i.e., reactivation from latency)
  - Persistent infection (replication competent vector)
- Safety monitoring: all subjects in clinical studies should be monitored
    - 15 years for integrating vectors/ genome editing products
    - 5 years for AAV vectors (replication incompetent)
- LTFU does not need to be as detailed as safety monitoring for initial trial
      - Survival, SAEs, delayed onset safety effects (heme, immune, neuro, onc)

FDA

Long Term Follow-Up After Administration of Human Gene Therapy Products

Guidance for Industry

emea European Medicines Agency

GUIDELINE ON FOLLOW-UP OF PATIENTS ADMINISTERED WITH GENE THERAPY MEDICINAL PRODUCTS

What is a Platform Trial?

- Complex and nonstandard study designs have grown in acceptance in recent years

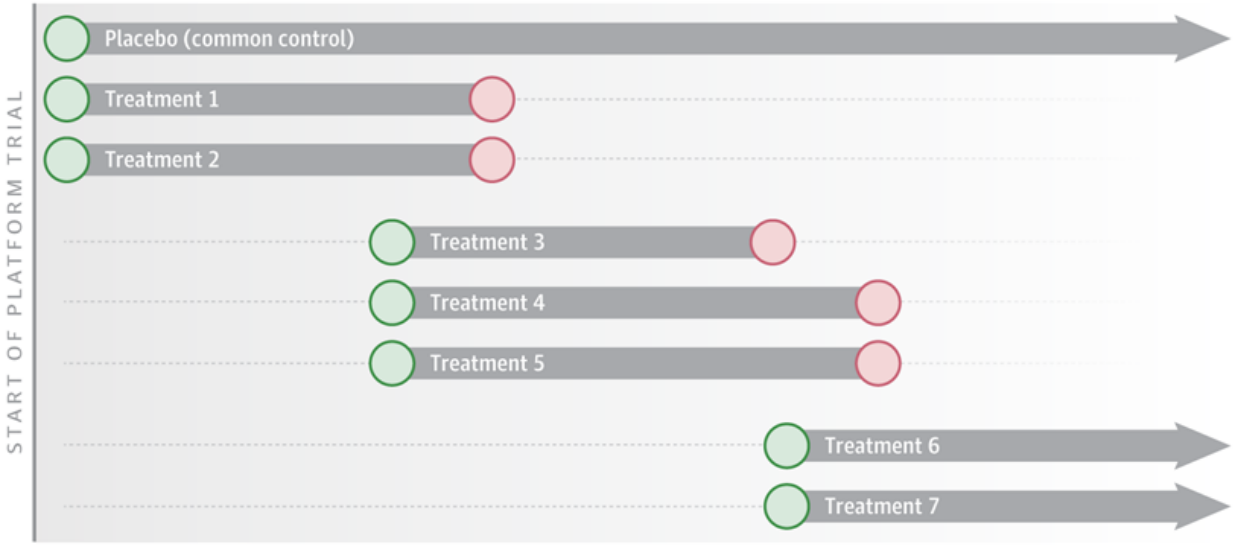
- Platform trials are the most flexible of the proposed designs, with patient groups or drug arms allowed to enter and exit the study in a predefined manner

- In the past these were used mostly oncology trials, but have recently expanded. Example: *the Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia* (**REMAP-CAP**), that investigated hydrocortisone vs no hydrocortisone for patients with severe COVID-19

Table 1. Types of Master Protocols.

Type of Trial	Objective
Umbrella	To study multiple targeted therapies in the context of a single disease
Basket	To study a single targeted therapy in the context of multiple diseases or disease subtypes
Platform	To study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm

Woodcock, Janet, and Lisa M. LaVange. "Master protocols to study multiple therapies, multiple diseases, or both." *New England Journal of Medicine* 377.1 (2017): 62-70.



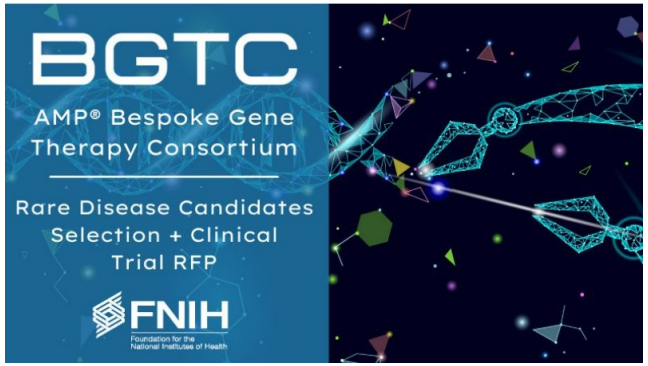
Park, Jay JH, et al. "How to Use and Interpret the Results of a Platform Trial: Users' Guide to the Medical Literature." *JAMA* 327.1 (2022): 67-74.

Bespoke Gene Therapy Consortium (BGTC)

Envision 4-6 test cases

Foundation for the National Institutes of Health
5,740 followers
1d • Edited •

AMP® BGTC is pleased to announce it has selected 14 rare disease candidates. In addition, a new RFP has been issued for clinical trial proposals directed to one of these 14 bespoke indications. Read the full selection announcement here: https://lnkd.in/gguU_whr



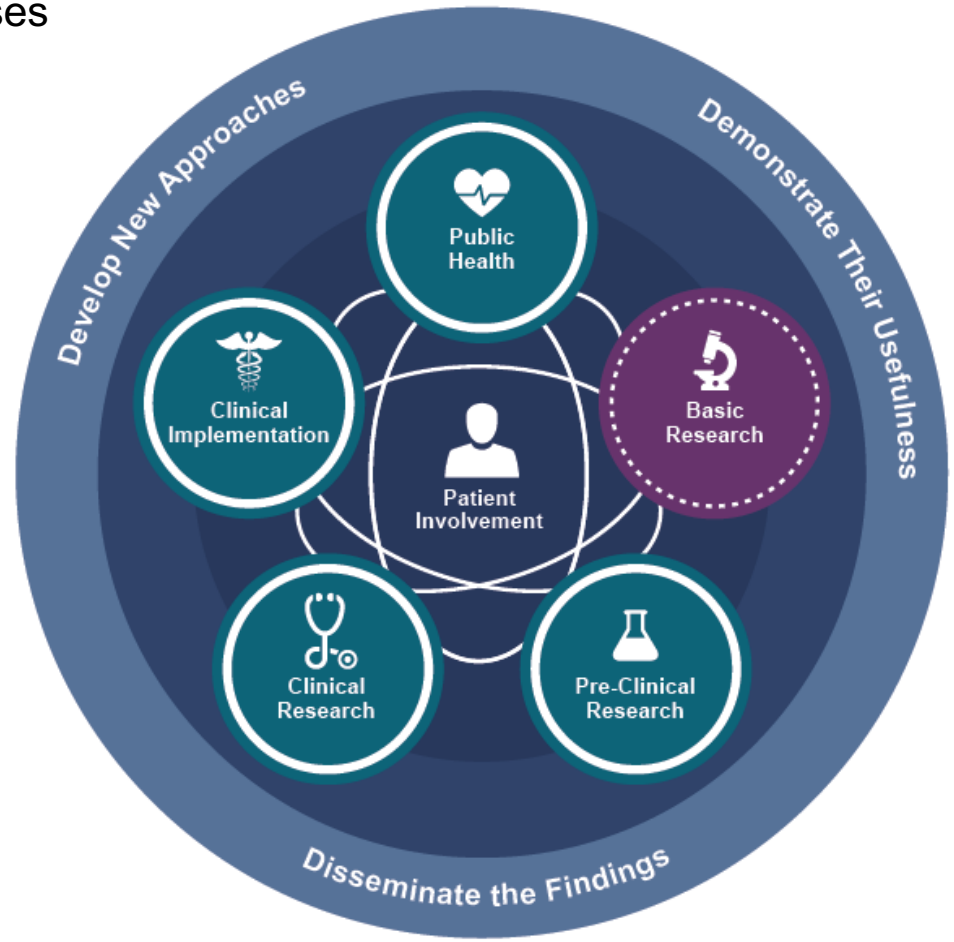
BGTC Goals

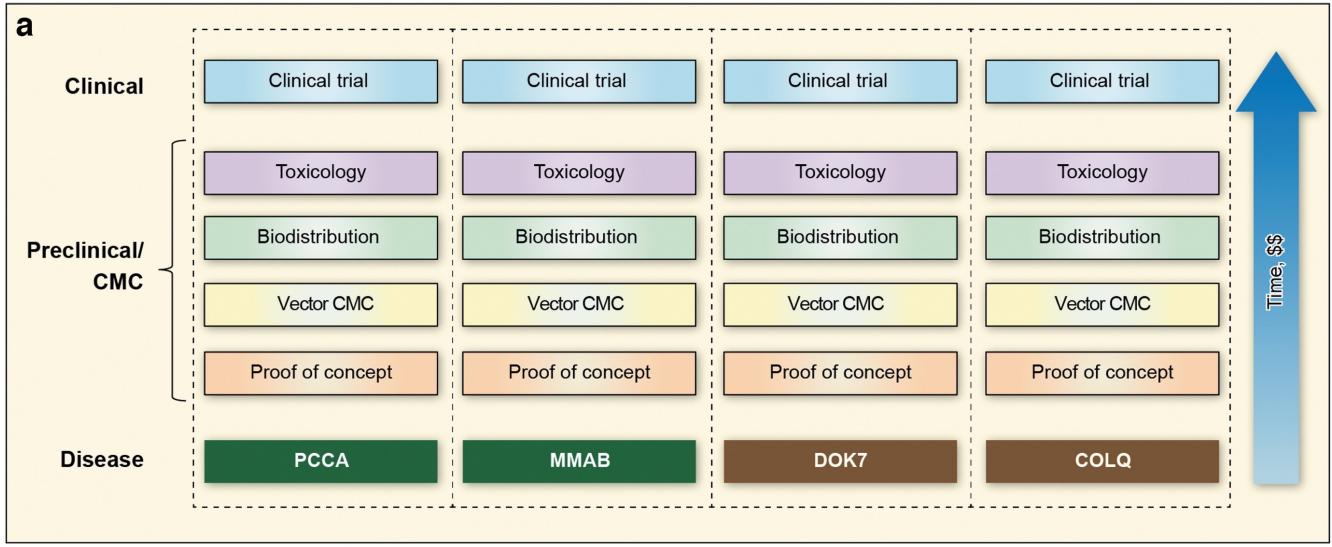
- Make adeno-associated virus technology more accessible to a broader range of diseases
  - Optimized AAV vector production protocols
  - Improvements in AAV target gene expression
- Streamline preclinical and product testing
  - Harmonized and validated sets of manufacturing and pre-clinical testing requirements
- Facilitate scientific and regulatory advances that will ultimately benefit the entire field
  - Standardized regulatory submission package templates
- Bring gene therapies to all affected populations sooner
  - Clinical development manual to help advance all future AAV gene therapies for rare diseases

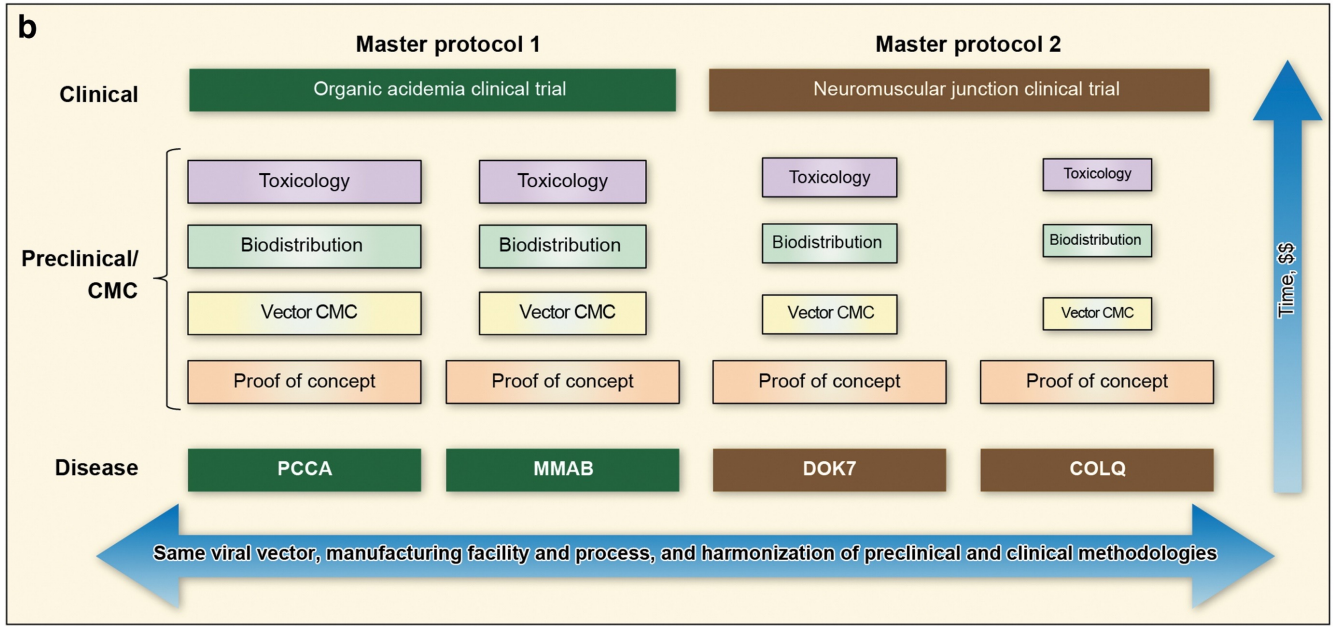
The Two Critical Pathways of BGTC Research

Platform Vector Gene Therapy (PaVe-GT)

Basic Questions of PaVe-GT: can efficiency of GTx development be increased by using a standardized platform process: same capsid and manufacturing, for four distinct diseases







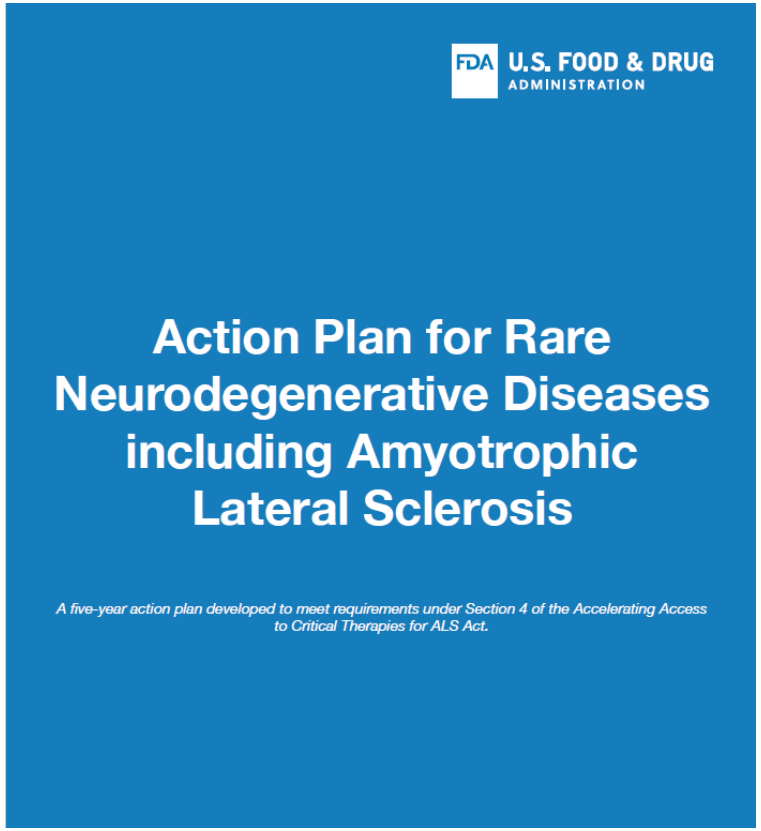
Recent FDA Initiatives Support this Approach to Safety

Cell and Gene Therapies Safety Project

FDA will review its experience with applications for ALS and rare neurodegenerative disorder treatments to identify cross-application safety signals, with a focus on factors such as the specific type of product (e.g., gene therapy, cell therapy, vector), route of administration, and study population (e.g., age, disease severity, clinical manifestations). FDA will use this safety information to inform the design of subsequent clinical trials for the use of cell and gene therapies to treat ALS and other neurodegenerative diseases.

Explore the Use of Fit-for-Purpose[13] Digital Health Technologies[14]

FDA will encourage exploring the use of digital health technologies to potentially improve understanding of the disease and increase access to investigational drugs through more accessible clinical trials. Using digital health technologies may enhance use of decentralized trial approaches that can increase trial participation and reduce the burden of trial participation on individuals with ALS and their caregivers. For example, digital health technologies may reduce the need for travel to study sites. These technologies may also be used to increase ability to monitor and assess drug response by providing a more comprehensive assessment of the rate of decline in the range of functional capabilities affected by ALS.



Why Have a Platform Safety Approach in LTFU?

- Rationale: the safety profile, including immediate and long-term toxicity and AAV integration/carcinogenesis potential should have some similarities, either across vector serotypes/cassettes (e.g., AAV9), or even across the entire class (all AAV), or perhaps within a given therapeutic area (e.g., heme, CNS, cardiac)

Scientific	Commercial/ geographies	Indication expansion	Reduce cycle times	Increase PoS for future submissions
Pooling standardized data (same assays, durations, aligned schedules of assessments for biopsies/ samples), both short term and long term, will enable **major** unanswered questions in GTx to be addressed	A more robust safety package for follow-on geographies can increase probability of success for HTA assessments and access	Health authorities may have fewer concerns about expansion into adjacent populations (older, younger, heavier, different phenotype) if there's robust and identifiable safety profile	Follow from left column: increased confidence in safety profile across a class can reduce or eliminate the clinical evidence needed for indication expansion	A more robust safety package for new products in a class could inform benefit-risk assessment during reg. review and increase probability of approval in a new but adjacent indication or modality

Comparing Apples to Apples

ARTICLE

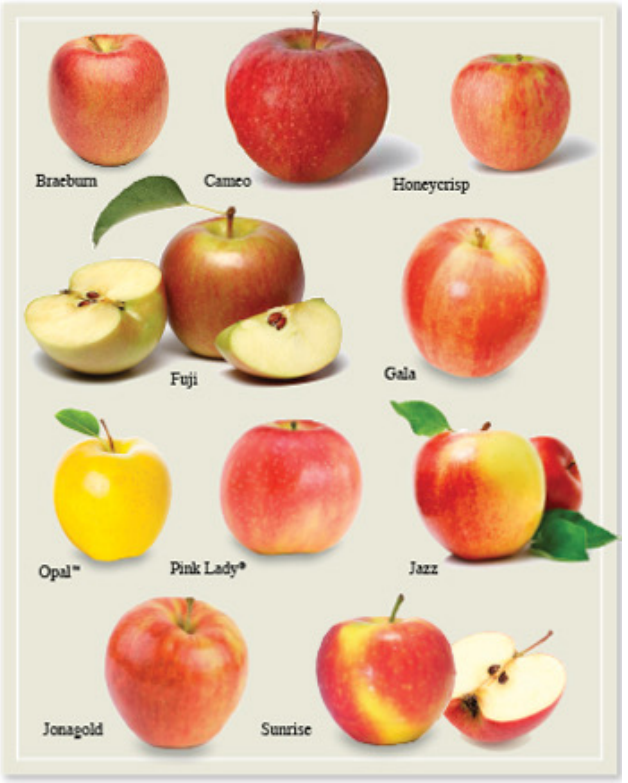
Standardized Data Structures in Rare Diseases: CDISC User Guides for Duchenne Muscular Dystrophy and Huntington's Disease

Ariana P. Mullin[1], Diane Corey[1], Emily C. Turner[1], Richard Liwski[1], Daniel Olson[1], Jackson Burton[1], Sudhir Sivakumaran[1], Lynn D. Hudson[1], Klaus Romero[1], Diane T. Stephenson[1] and Jane Larkindale[1,*]

The principle of standardization to increase efficiency is well described in the rare disease space

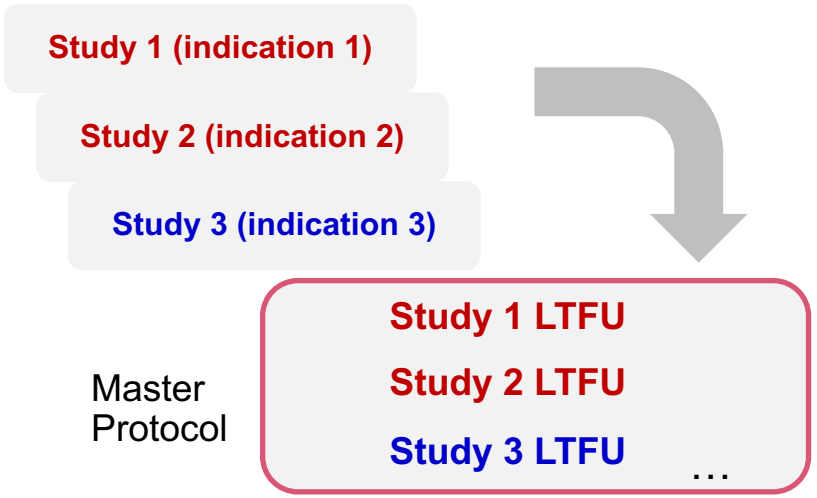
We need to be able to compare biosamples from identical assays, collected in an identical manner, during an identical time course (schedule of assessments)

CDISC—CPATH efforts in this spirit are instructional



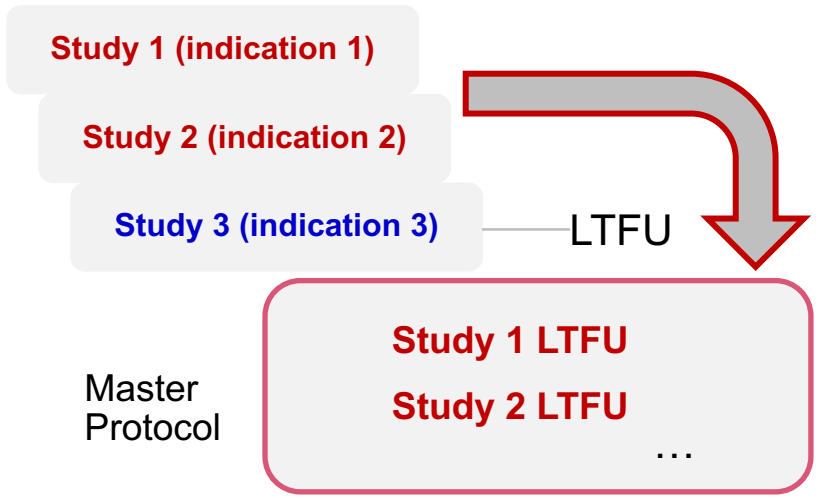
Platform Opportunities for Long-Term Follow-Up (LTFU) of Gene Therapies for Robust Assessments of Safety

Scope	Multiple therapies in heterogeneous populations; explicitly assumes safety may be heterogeneous
Duration	Open ended, with study populations entering and exiting as available/ complete
Number of groups	Any number of studies with only treated subjects
Assessment of safety signals	May or may not be transferrable from one population/ modality to the next
Schedule of assessments	Could be individually tailored by study, standardized across studies, or shared core SoA with appendices for given diseases
Sponsor support	Could be single sponsor, or cross-industry consortium



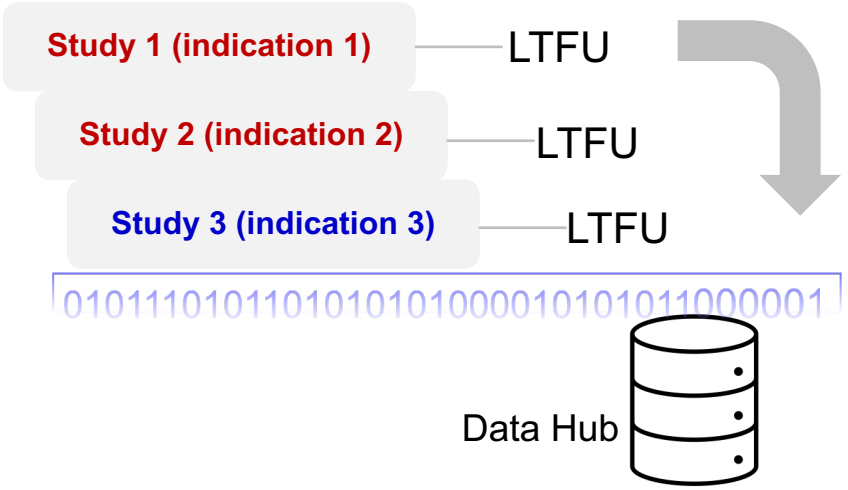
Case 1: Pool multiple LTFU GTx studies

- Can harmonize SoAs, CRFs across studies, modalities/ constructs, indication classes
- Opportunities for alignment at a high level



Case 2: Pool *select* LTFU GTx studies

- Can harmonize SoAs, CRFs across studies within an indication class
- Could have multiple platforms per indication



Case 3: Pool data from LTFU studies in a hub

- Eliminates total harmonization of assessments, but opportunities for data pooling still possible with workarounds, limitations

CRF = Case report form; GT = Gene therapy; LTFU = Long-term follow up; SoA = Schedule of assessment.

Platform Trials for LTFU Allow Adaptivity in CDPs

Scientific	Pooling standardized data can address major unanswered safety questions (e.g., same assays, durations, aligned schedules of assessments for biopsies / samples)
Patient Access	A robust safety package for follow-on geographies can enhance HTA dossiers for successful reimbursement / access
Efficiency	Increased regulator confidence in safety across a therapeutic class can reduce the clinical evidence needed for adjacent populations (e.g., older, younger, different phenotype)
Pharmacologic	Clinical pharmacology models of exposure, persistence, and other dynamic parameters can be informed by longer term human data pooled across appropriate classes
Future Development	Robust safety for new products in a class (e.g., gene editing) could inform benefit-risk and increase likelihood of approval in new but adjacent indications / modality

How /Why to Pool AE Rates Across a Class for GTx

- The European Commission's guideline on summary product characteristics (SmPC) classifies AEs in five frequency categories:
  - very rare (< 0.01%)
  - rare (< 0.1%)
  - uncommon (< 1%)
  - common (< 10%)
  - very common (≥ 10%)

- Accurate estimation of anything but "very common" and "common" is infeasible for LTFU trials that may have < 100 subjects

- The key to this limitation is in statistical tools that "borrow strength" from similar categories within a cluster

Bayesian Hierarchical Modeling (BHM)

- Hierarchical statistical models are appropriate when there is more than one level of structure or hierarchy in the data
- Strong scientific rationale to support the hypothesis that classes of gene therapy products have similar adverse event profiles:
  - Mechanism of action
  - Route of administration
  - Vector
- **For a platform trial containing related sub-studies, we should borrow information on adverse event rates (where appropriate)**
- Bayesian modeling is well-suited to hierarchical models because prior knowledge can inform the degree of information borrowing and MCMC methods can fit complex models

Neuenschwander, B., Wandel, S., Roychoudhury, S., & Bailey, S. (2016). Robust exchangeability designs for early phase clinical trials with multiple strata. *Pharmaceutical statistics*, *15*(2), 123-134.

EXNEX

- In BHMs, sharing is determined by how much data was collected in each trial
  - Trials with less data borrow more strongly from the other trials

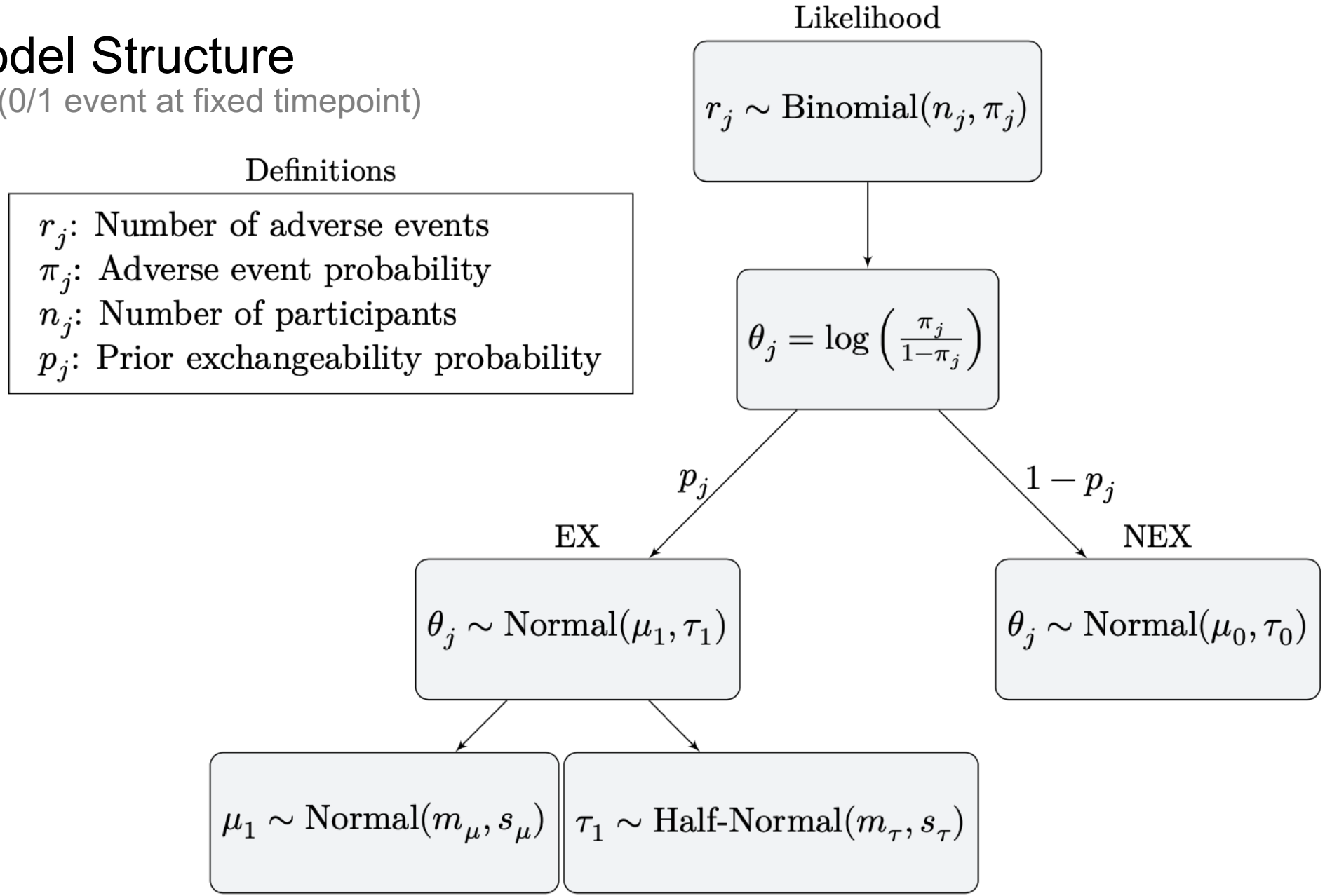
- Bayesian hierarchical models:
  - Perform well when the trials are “exchangeable” (i.e., cluster around a common rate)
  - Perform poorly if any of the trials has an extreme event rate compared to the others

- **EXNEX** (“Exchangeable/Non-Exchangeable”) is an extension of BHMs that is more robust to outlier clusters
  - Mixture model where each trial is “exchangeable” with the others in platform with probability p_j or not exchangeable with *any* with probability (1- p_j)

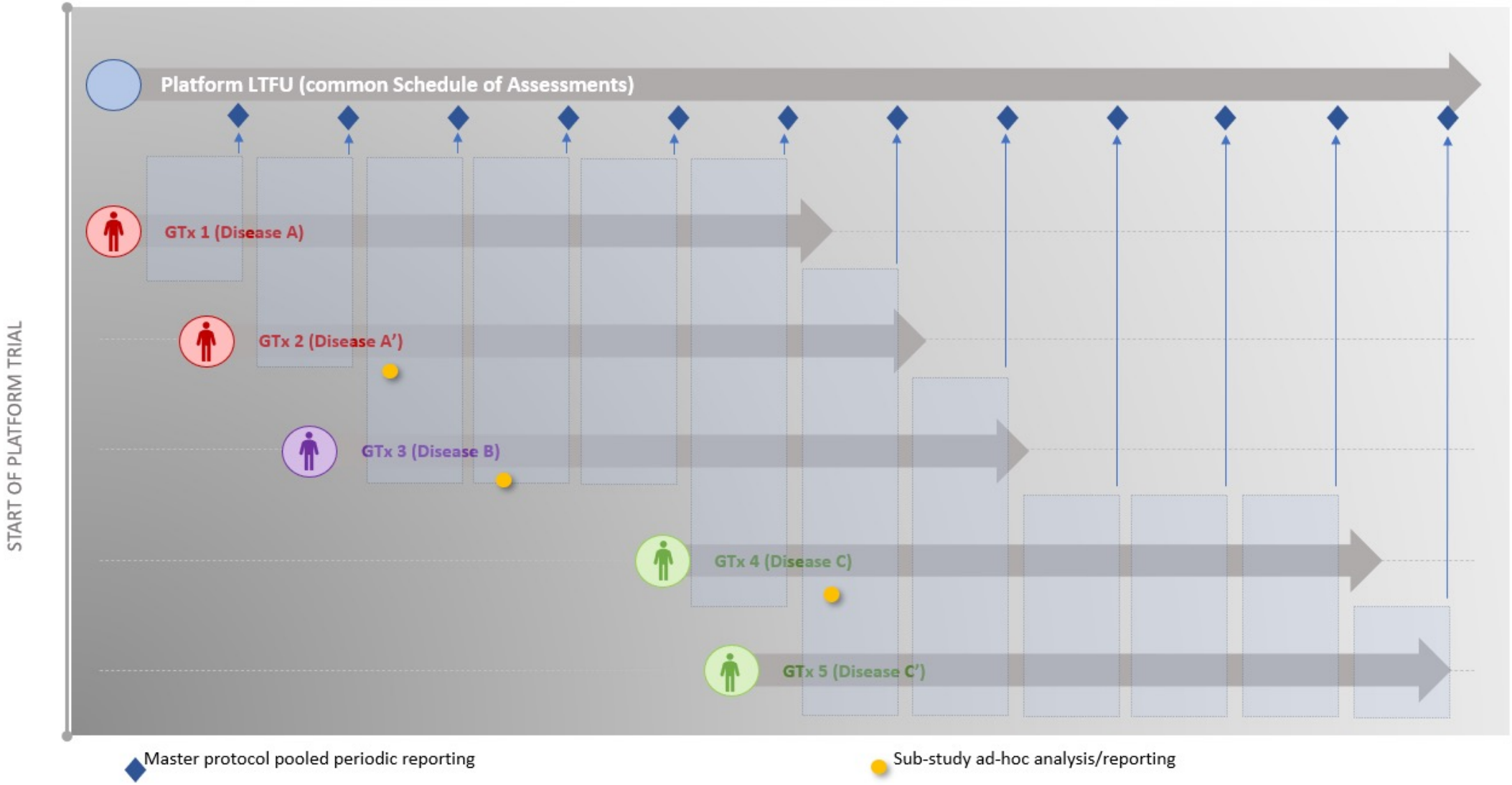
Neuenschwander, B., Wandel, S., Roychoudhury, S., & Bailey, S. (2016). Robust exchangeability designs for early phase clinical trials with multiple strata. *Pharmaceutical statistics*, *15*(2), 123-134.

EXNEX Model Structure

Binary outcome (0/1 event at fixed timepoint)

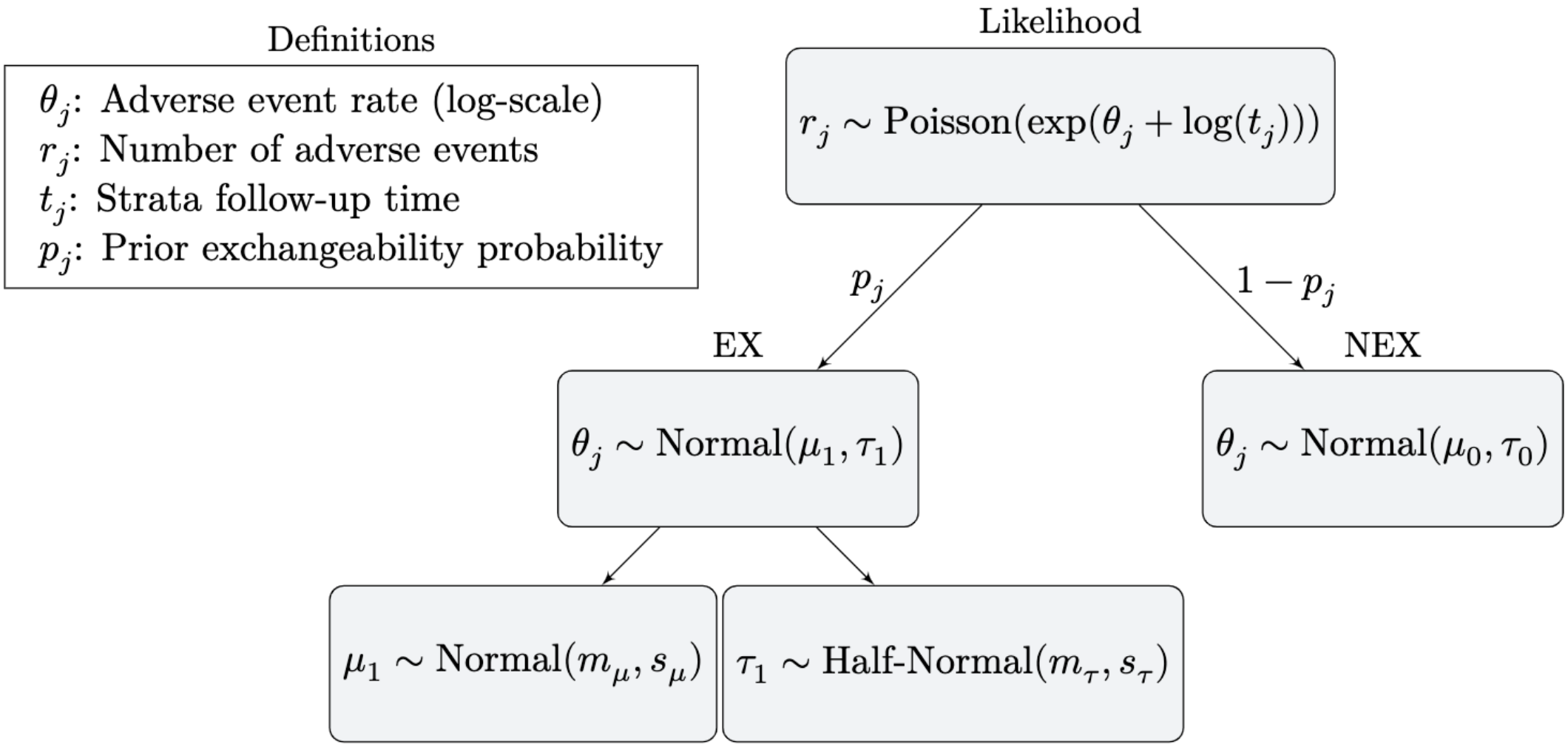


Adverse Events with Varying Follow-Up Times



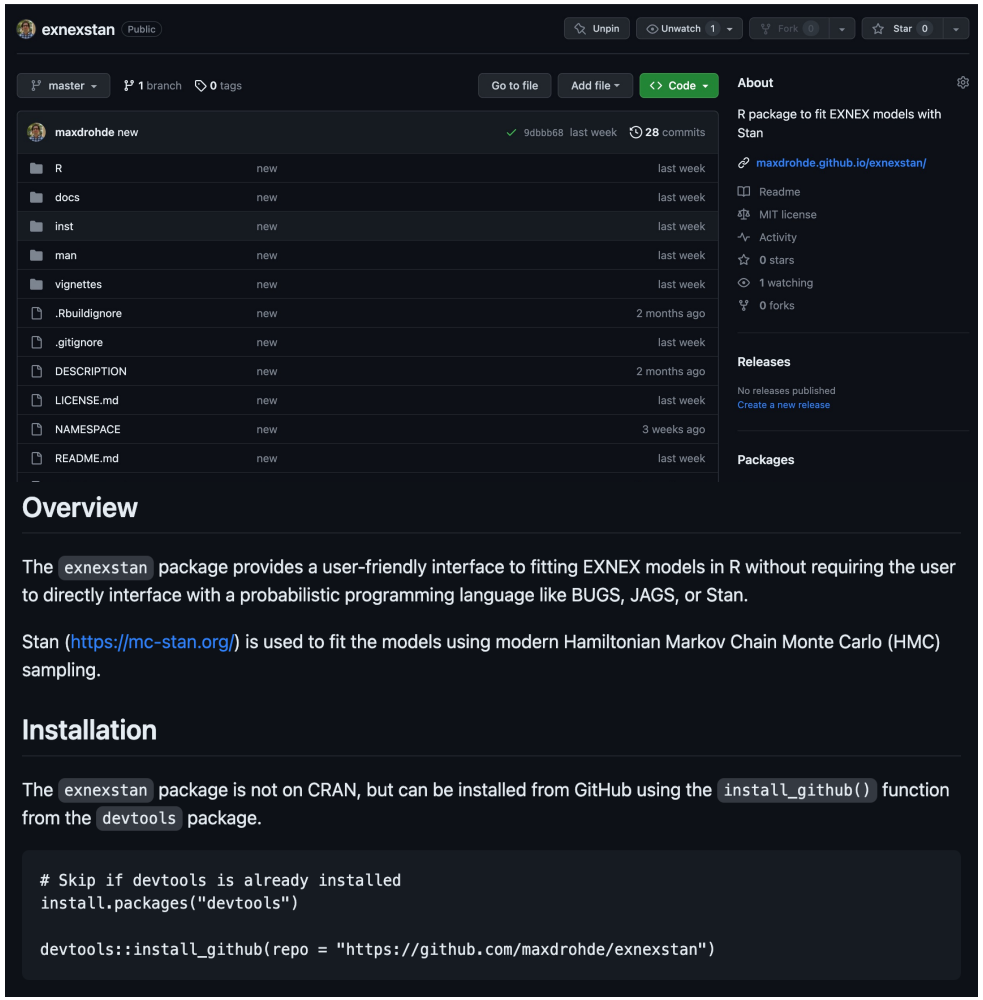
EXNEX Model Structure

Count outcome (use *offset* for varying follow-up times)



Fitting EXNEX models with the *exnexstan* R package

GitHub page



exnexstan Public

Unpin | Unwatch 1 | Fork 0 | Star 0

master | 1 branch | 0 tags | Go to file | Add file | Code

maxdrohde new — 9dbbb68 last week — 28 commits

R	new	last week
docs	new	last week
inst	new	last week
man	new	last week
vignettes	new	last week
.Rbuildignore	new	2 months ago
.gitignore	new	last week
DESCRIPTION	new	2 months ago
LICENSE.md	new	last week
NAMESPACE	new	3 weeks ago
README.md	new	last week

About

R package to fit EXNEX models with Stan

maxdrohde.github.io/exnexstan/

Readme
MIT license
Activity
0 stars
1 watching
0 forks

Releases

No releases published
Create a new release

Packages

Overview

The `exnexstan` package provides a user-friendly interface to fitting EXNEX models in R without requiring the user to directly interface with a probabilistic programming language like BUGS, JAGS, or Stan.

Stan (https://mc-stan.org/) is used to fit the models using modern Hamiltonian Markov Chain Monte Carlo (HMC) sampling.

Installation

The `exnexstan` package is not on CRAN, but can be installed from GitHub using the `install_github()` function from the `devtools` package.

```
# Skip if devtools is already installed
install.packages("devtools")

devtools::install_github(repo = "https://github.com/maxdrohde/exnexstan")
```

R package vignettes

`exnexstan`: Binary data and package overview

</> Code

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Background

The `exnexstan` package implements the EXNEX model for binary data introduced in "Robust exchangeability designs for early phase clinical trials with multiple strata" by Neuenschwander et al. (2015) (https://onlinelibrary.wiley.com/doi/10.1002/pst.1730) using Stan. The `cmdstanr` package is used to interface R with the Stan probabilistic programming language that fits the models using Markov Chain Monte Carlo (MCMC)[1].

EXNEX models are an extension of Bayesian hierarchical models (BHMs). Bayesian hierarchical models are commonly used to analyze data from related studies, such as strata in a basket trial, since the partial pooling resulting from BHMs is often a good compromise between complete stratification and complete pooling. However, BHMs can perform poorly if some strata are not exchangeable with the other strata.

EXNEX is a mixture model that allows for each strata the possibility of being exchangeable (with probability p_j) with the other strata, or nonexchangeable with the other strata (with probability (1 - p_j)). This increases the robustness of the model to certain strata being not exchangeable with the others. More than two exchangeability groups may be specified in the model, although they can be difficult to fit depending on the amount of data available. Currently, `exnexstan` only supports a single exchangeability group.

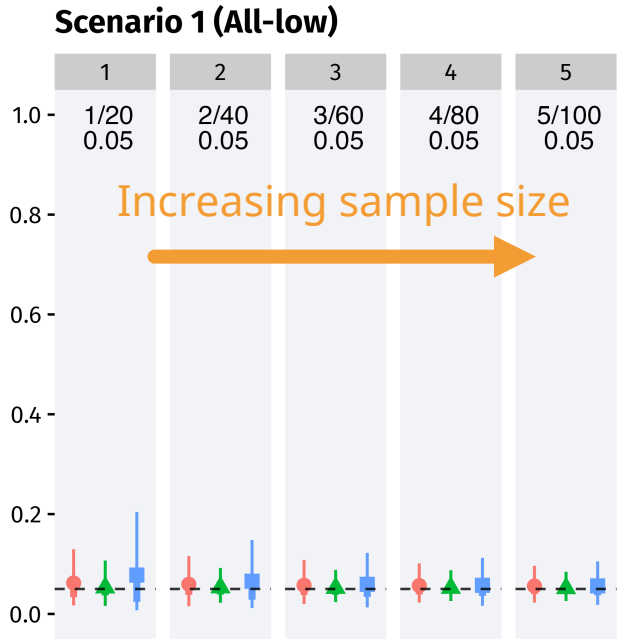
We write out the model in mathematical notation below. For clarity, we use the names for the prior values as given in the code.

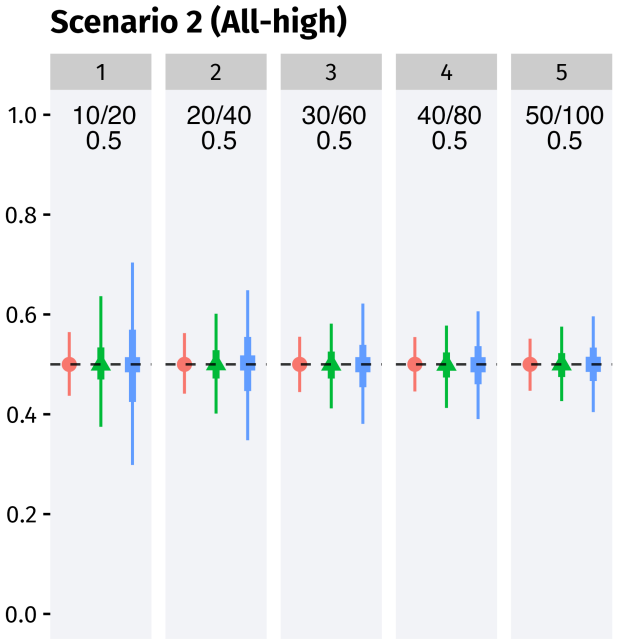
$$
\begin{aligned}
Z_j &\sim \text{Bernoulli}(p_j) && \text{(Indicator variable of EX vs NEX)} \\
\theta_j &\sim \text{Normal}(\text{mean} = \mu_{Z_j}, \text{sd} = \tau_{Z_j}) && \text{(Response probability on log-odds scale)} \\
\mu_0 &= \texttt{nex\_prior\_mean} && \text{(NEX mean)} \\
\tau_0 &= \texttt{nex\_prior\_sd} && \text{(NEX standard deviation)}
\end{aligned}
$$

EXNEX Scenario

Binary outcome

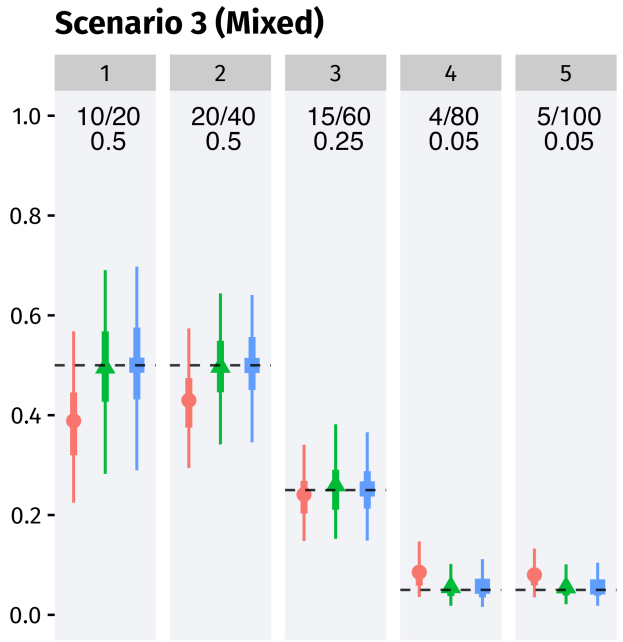
- 1,2,3,4,5 columns are platform sub-studies
- Numbers at top of each column are #AEs / cohort sample size, and associated rate
- Dotted lines are true event rate

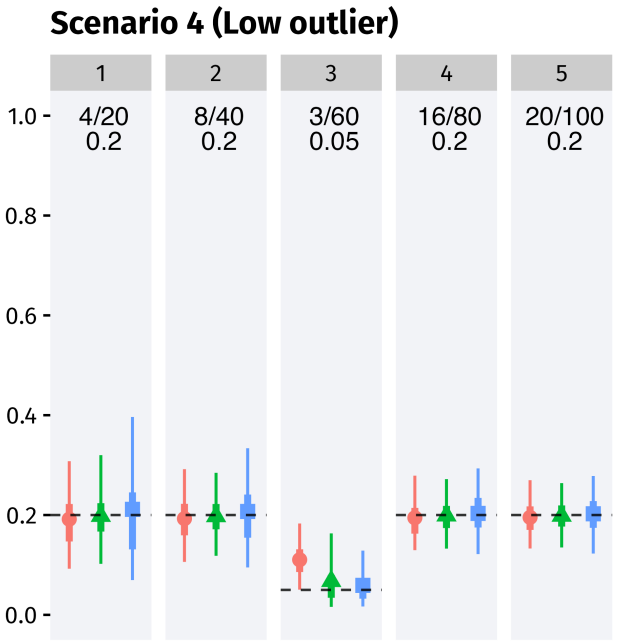


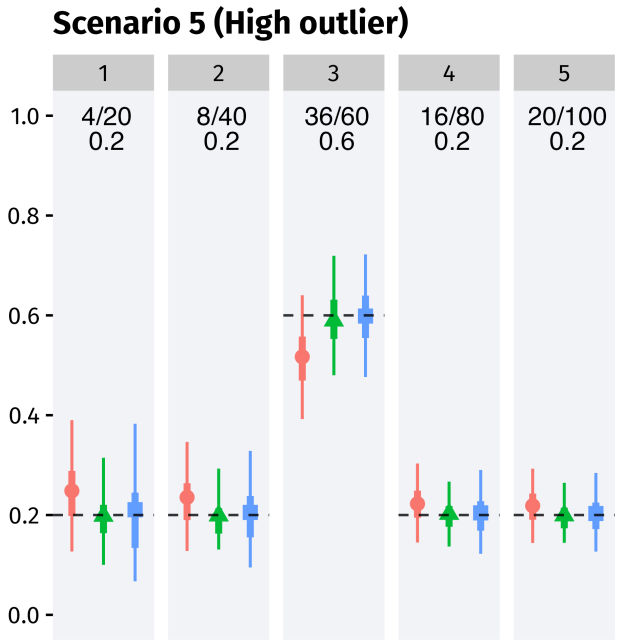


- Smaller credible intervals vs stratified models
- Outlier scenario estimates still resemble true rate (unlike some EX models)

Exchangeable (EX)
EXNEX
Stratified (NEX)







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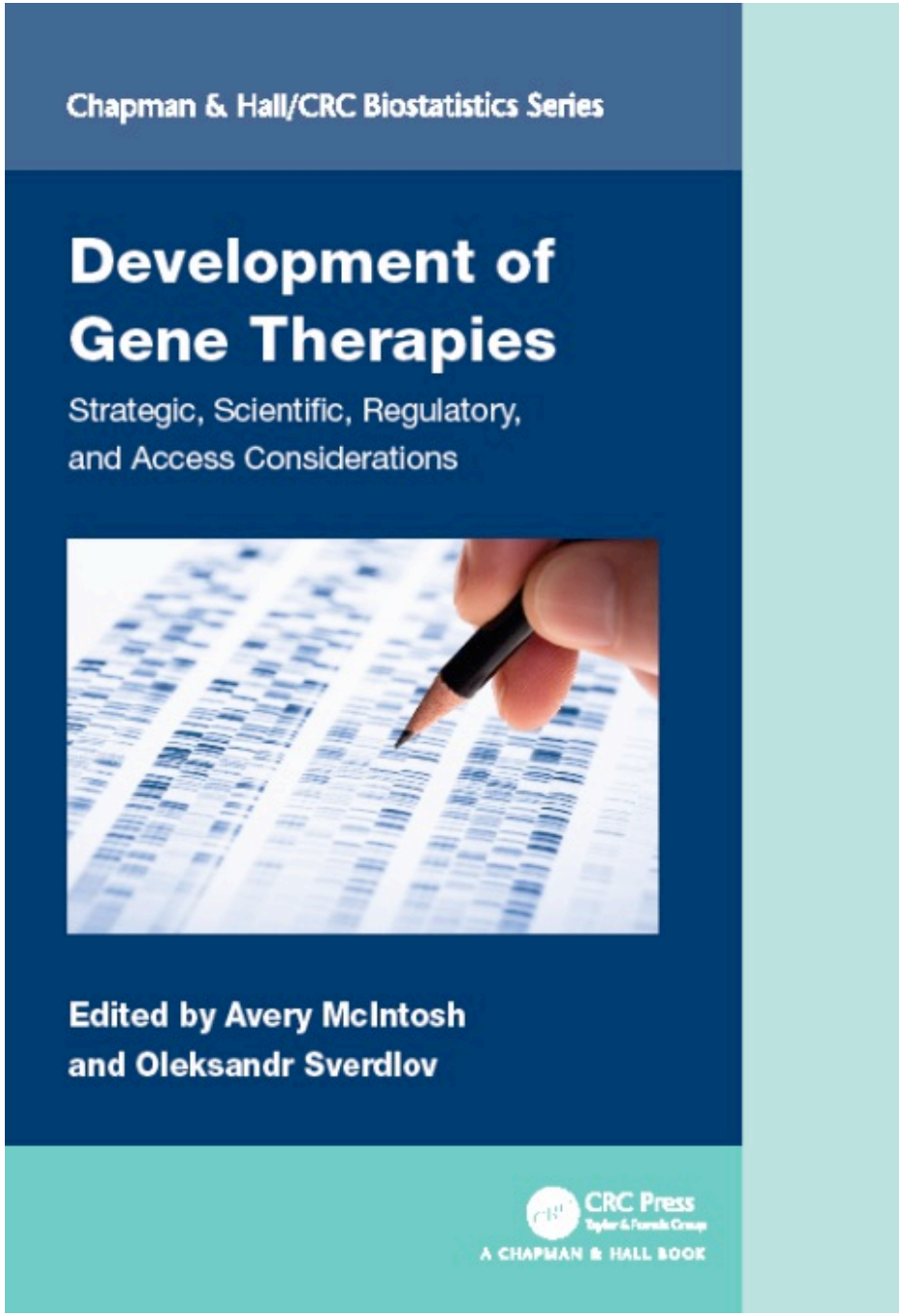

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Clinical Pharmacology & Therapeutics

ANNALS of Clinical and Translational Neurology